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(57) Abstract

Microchips are provided, which control both the rate and time of release of multiple chemical substances and which allow for the release of a wide variety of molecules in either a continuous or pulsatile manner. In all of the preferred embodiments, a material that is impermeable to the drugs or other molecules to be delivered and the surrounding fluids is used as the substrate. Reservoirs are etched into the substrate using either chemical (wet) etching or ion beam (dry) etching techniques well-known in the field of microfabrication. Hundreds to thousands of reservoirs can be fabricated on a single microchip using these techniques. A release system, which includes the molecules to be delivered, is inserted into the reservoirs by injection, inkjet printing or spin coating methods. Exemplary release systems include polymers and polymeric matrices, non-polymeric matrices, and other excipients or diluents. The physical properties of the release system control the rate of release of the molecules. The reservoirs can contain multiple drugs or other molecules in variable dosages. The filled reservoirs can be capped with materials that either degrade, dissolve, or allow the molecules to diffuse passively out of the reservoir over time or materials that, upon application of an electric potential, oxidize to form soluble compounds or ions that dissolve into the surrounding fluids. Release from an active device can be controlled by a preprogrammed microprocessor, remote control, or by biosensors.

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MICROCHIP DRUG DELIVERY DEVICES

Background of the Invention

This invention relates to miniaturized drug delivery devices and more particularly, to controlled time and rate release multi-welled drug delivery devices.

Drug delivery is an important aspect of medical treatment. The efficacy of many drugs is directly related to the way in which they are administered. Some therapies require that the drug be repeatedly administered to the patient over a long period of time. This makes the selection of a proper drug delivery method problematic. Patients often forget, are unwilling, or are unable to take their medication. Drug delivery also becomes problematic when the drugs are too potent for systemic delivery. Therefore, attempts have been made to design and fabricate a delivery device which is capable of the controlled, pulsatile or continuous release of a wide variety of molecules including, but not limited to, drugs and other therapeutics.

Controlled release polymeric devices have been designed to provide drug release over a period of time via diffusion of the drug out of the polymer and/or degradation of the polymer over the desired time period following administration to the patient. However, these devices are relatively simple.

U.S. Patent No. 5,490,962 to Cima, et al. discloses the use of three dimensional printing methods to make more complex devices which provide release over a desired time frame, of one or more drugs. Although the general procedure for making a complex device is described, specific designs are not detailed.

U.S. Patent No. 4,003,379 to Ellinwood describes an implantable electromechanically driven device that includes a flexible retractable walled container, which receives medication from a storage area via an inlet and then dispenses the medication into the body via an outlet. U.S. Patent No. 4,146,029 and U.S. Patent No. 3,692,027 to Ellinwood

disclose self-powered medication systems that have programmable miniaturized dispensing means. U.S. Patent No. 4,360,019 to Jassawalla discloses an implantable infusion device that includes an actuating means for delivery of the drug through a catheter. The actuating means includes a solenoid driven miniature pump. All of these devices include miniature power-driven mechanical parts that are required to operate in the body, i.e., they must retract, dispense, or pump. These are complicated and subject to breakdown. Moreover, due to complexity and size restrictions, they are unsuitable to deliver more than a few drugs or drug mixtures at a time.

It is therefore an object of the present invention to provide a simple to use and manufacture, dependable, multi-welled delivery device for drugs and other molecules which can operate for weeks or years at a time.

It is another object of the present invention to provide such a device that allows delivery of drugs or other molecules in either a pulsatile or continuous manner.

It is yet another object of the present invention to provide such a device that allows the delivery to be controlled either passively or actively.

It is also an object of the present invention to provide such a device that can hold many different drugs or other molecules of varying dosages and is small enough to be implanted, injected or swallowed, if desired.

Summary of the Invention

Microchips for delivery of a wide variety of molecules are provided. Microchips are miniaturized devices constructed using methods commonly applied to the manufacture of integrated circuits such as ultraviolet (UV) photolithography, reactive ion etching, and electron beam evaporation. The microchips provide control over the rate the molecules

are released as well as the time at which release begins. The time of release can be controlled passively or actively.

In the preferred embodiments, a material which is impermeable to the surrounding fluids and to the molecules to be delivered is used as the substrate. Examples of substrate materials include ceramics, semiconductors such as silicon, and degradable and non-degradable polymers. Reservoirs are etched into the substrate using either chemical (wet) etching or ion (dry) etching techniques commonly used in microfabrication. Hundreds to thousands of reservoirs can be created in this manner and contained in a single microchip. Typically, a release system containing, encapsulating, or consisting of the molecule to be delivered is inserted into the reservoirs by injection, inkjet printing, or other means. The release system controls the rate of release of the molecule. The rate of release is a function of the composition and structure of the release system. The device design makes it possible to fill the reservoirs with a release system in solid, liquid, or gel form. Each of the reservoirs of a single microchip can contain different molecules and/or different amounts and concentrations, which can be released independently.

In a preferred embodiment, the reservoir cap enables passive timed release, not requiring a power source, of molecules. The reservoirs are capped with materials that degrade or dissolve at a known rate or have a known permeability (diffusion constant) for the molecules to be delivered. Therefore, the degradation, dissolution or diffusion characteristics of the cap material determine the time at which the release of molecules in a particular reservoir begins. In effect, the microchip provides dual control of the release of molecules by selection of the release system (rate controller) and selection of the cap material (time controller, and in some cases, rate controller).

In another preferred embodiment, the reservoir cap enables active timed release, requiring a power source, of molecules. In this embodiment, the reservoir caps consist of a thin film of conductive

material that is deposited over the reservoir, patterned to a desired geometry, and serves as an anode. Cathodes are also fabricated on the device with their size and placement dependent on the device's application and method of electric potential control. Conductive materials capable of dissolving into solution or forming soluble compounds or ions upon the application of an electric potential, including metals such as copper, gold, silver, and zinc and some polymers, are used in the active timed release device. When an electric potential is applied between an anode and cathode, the conductive material of the anode above the reservoir oxidizes to form soluble compounds or ions that dissolve into solution, exposing the release system containing the molecules to be delivered to the surrounding fluids. Alternatively, the application of an electric potential can be used to create changes in local pH near the anode reservoir cap to allow normally insoluble ions or oxidation products to become soluble. This would allow the reservoir to dissolve and expose the release system to the surrounding fluids. In either case, the molecules to be delivered are released into the surrounding fluids by diffusion out of or by degradation or dissolution of the release system. The frequency of release is controlled by incorporation of a miniaturized power source and microprocessor onto the microchip. Activation of any reservoir can be achieved by preprogramming the microprocessor, by remote control, or by a signal from a biosensor.

Description of the Drawings

Figure 1 depicts a typical fabrication scheme for a passive delivery device.

Figure 2 depicts a typical fabrication scheme for an active delivery device.

Figure 3 depicts a typical device control circuitry flowsheet.

Figure 4 depicts a passive delivery device.

Figure 5 depicts an active delivery device.

Figure 6 depicts an active device including insulator overlayers.

Figures 7a-i are schematic views of several configurations of passive delivery devices.

Figures 8a-c are schematic views of several configurations of active delivery devices.

Detailed Description

Microchip devices have been provided which can accurately deliver drugs and other molecules at defined rates and times according to the needs of the patient or other experimental system. As used herein, a "microchip" is a miniaturized device fabricated using methods commonly applied to the manufacture of integrated circuits such as ultraviolet (UV) photolithography, reactive ion etching, and electron beam evaporation, as described, for example, by S. Wolf and R.N. Tauber, *Silicon Processing for the VLSI Era, Volume 1 - Process Technology*, Lattice Press, Sunset Beach, CA, 1986; and R.C. Jaeger, *Introduction to Microelectronic Fabrication*, Volume V in the Modular Series on Solid State Devices, Addison-Wesley, Reading, MA, 1988. The microchips provide control over the rate the molecules are released as well as the time at which release begins. The time of release can be controlled passively or actively. The microchip fabrication procedure allows the manufacture of devices with primary dimensions (length of a side if square or rectangular, or diameter if circular) ranging from a few millimeters to several centimeters. A typical device thickness is 300 μm. However, the thickness of the device can vary from approximately 10 μm to several millimeters. Changing the device thickness affects the maximum number of reservoirs that may be incorporated onto a microchip and the volume of each reservoir. *In vivo* applications of the device would typically require devices having a primary dimension of 2 cm or smaller. Devices for *in vivo* applications are small enough to be swallored or implanted using minimally invasive procedures. Smaller *in vivo* devices (on the order of a millimeter) can be implanted using a catheter or other

injectable means. Devices for *in vitro* applications have fewer size restrictions and, if necessary, can be made much larger than the dimension ranges for *in vivo* devices.

MATERIALS FOR DEVICE FABRICATION

Each device consists of a substrate, reservoirs, and a release system containing, enclosing, or layered with the molecules to be delivered. Devices which control the release time of the molecules may include reservoir caps. Active devices may include control circuitry and a power source.

The substrate

The substrate contains the etched or machined reservoirs and serves as the support for the microchip. Any material which can serve as a support, is suitable for etching or machining, and is impermeable to the molecules to be delivered and to the surrounding fluids, for example, water, blood, electrolytes or other solutions, may be used as a substrate. Biocompatibility of the substrate material is preferred, but not required. For *in vivo* applications, non-biocompatible materials may be encapsulated in a biocompatible material, such as poly(ethylene glycol) or polytetrafluoroethylene-like materials, before use. One example of a strong, non-degradable, easily etched substrate that is impermeable to the molecules to be delivered and the surrounding fluids is silicon. In another embodiment, the substrate is made of a strong material that degrades or dissolves over a period of time into biocompatible components. This embodiment is preferred for *in vivo* applications where the device is implanted and physical removal of the device at a later time is not feasible or recommended, for example, brain implants. An example of a class of strong, biocompatible materials are the poly(anhydride-*co*-imides), discussed by K.E. Uhrich *et al.*, "Synthesis and characterization of degradable poly(anhydride-*co*-imides)", *Macromolecules*, **1995**, 28, 2184-93.

Release system

The molecules to be delivered may be inserted into the reservoirs in their pure form, as a liquid solution or gel, or they may be encapsulated within or by a release system. As used herein, "release system" includes both the situation where the molecules are in pure form, as either a solid or liquid, or are in a matrix formed of degradable material or a material which releases incorporated molecules by diffusion out of or disintegration of the matrix. The molecules can be sometimes contained in a release system because the degradation, dissolution or diffusion properties of the release system provide a method for controlling the release rate of the molecules. The molecules can be homogeneously or heterogeneously distributed within the release system. Selection of the release system is dependent on the desired rate of release of the molecules. Both non-degradable and degradable release systems can be used for delivery of molecules. Suitable release systems include polymers and polymeric matrices, non-polymeric matrices, or inorganic and organic excipients and diluents such as, but not limited to, calcium carbonate and sugar. Release systems may be natural or synthetic, although synthetic release systems are preferred due to the better characterization of release profiles. The release system is selected based on the period over which release is desired, generally in the range of at least three to twelve months for *in vivo* applications. In contrast, release times as short as a few seconds may be desirable for some *in vitro* applications. In some cases, continuous (constant) release from a reservoir may be most useful. In other cases, a pulse (bulk) release from a reservoir may provide more effective results. Note that a single pulse from one reservoir can be transformed into pulsatile release by using multiple reservoirs. It is also possible to incorporate several layers of a release system and other materials into a single reservoir to achieve pulsatile delivery from a single reservoir. Continuous release can be achieved by incorporating a release system that degrades, dissolves, or allows diffusion of molecules through

it over an extended period of time. In addition, continuous release can be stimulated by releasing several pulses of molecules in quick succession.

The release system material can be selected so that molecules of various molecular weights are released from a reservoir by diffusion out or through the material or degradation of the material. Biodegradable polymers, bioerodible hydrogels, and protein delivery systems are preferred for release of molecules by diffusion, degradation, or dissolution. In general, these materials degrade or dissolve either by enzymatic hydrolysis or exposure to water *in vivo* or *in vitro*, or by surface or bulk erosion. Representative synthetic, biodegradable polymers include: poly(amides) such as poly(amino acids) and poly(peptides); poly(esters) such as poly(lactic acid), poly(glycolic acid), poly(lactic-*co*-glycolic acid), and poly(caprolactone); poly(anhydrides); poly(orthoesters); poly(carbonates); and chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), copolymers and mixtures thereof.

Representative synthetic, non-degradable polymers include: poly(ethers) such as poly(ethylene oxide), poly(ethylene glycol), and poly(tetramethylene oxide); vinyl polymers - poly(acrylates) and poly(methacrylates) such as methyl, ethyl, other alkyl, hydroxyethyl methacrylate, acrylic and methacrylic acids, and others such as poly(vinyl alcohol), poly(vinyl pyrolidone), and poly(vinyl acetate); poly(urethanes); cellulose and its derivatives such as alkyl, hydroxyalkyl, ethers, esters, nitrocellulose, and various cellulose acetates; poly(siloxanes); and any chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), copolymers and mixtures thereof.

Molecules to be released

Any natural or synthetic, organic or inorganic molecule or mixture thereof can be delivered. In one embodiment, the microchip is used to deliver drugs systemically to a patient in need thereof. In another embodiment, the construction and placement of the microchip in a patient enables the localized release of drugs that may be too potent for systemic delivery. As used herein, drugs are organic or inorganic molecules, including proteins, nucleic acids, polysaccharides and synthetic organic molecules, having a bioactive effect, for example, anaesthetics, vaccines, chemotherapeutic agents, hormones, metabolites, sugars, immunomodulators, antioxidants, ion channel regulators, and antibiotics. The drugs can be in the form of a single drug or drug mixtures and can include pharmaceutically acceptable carriers. In another embodiment, molecules are released *in vitro* in any system where the controlled release of a small (milligram to nanogram) amount of one or more molecules is required, for example, in the fields of analytic chemistry or medical diagnostics. Molecules can be effective as pH buffering agents, diagnostic agents, and reagents in complex reactions such as the polymerase chain reaction or other nucleic acid amplification procedures.

Reservoir caps

In the passive timed release drug delivery devices, the reservoir caps are formed from a material that degrades or dissolves over time, or does not degrade or dissolve but is permeable to the molecules to be delivered. These materials are preferably polymeric materials. Materials can be selected for use as reservoir caps to give a variety of degradation rates or dissolution rates or permeabilities to enable the release of molecules from different reservoirs at different times and, in some cases, different rates. To obtain different release times (amounts of release time delay), caps can be formed of different polymers, the same polymer with different degrees of crosslinking, or a UV polymerizable polymer. In the latter case, varying the exposure of this polymer to UV light results in varying degrees of crosslinking and gives the cap material different

diffusion properties or degradation or dissolution rates. Another way to obtain different release times is by using one polymer, but varying the thickness of that polymer. Thicker films of some polymers result in delayed release time. Any combination of polymer, degree of crosslinking, or polymer thickness can be modified to obtain a specific release time or rate. In one embodiment, the release system containing the molecules to be delivered is covered by a degradable cap material which is nearly impermeable to the molecules. The time of release of the molecules from the reservoir will be limited by the time necessary for the cap material to degrade or dissolve. In another embodiment, the cap material is non-degradable and is permeable to the molecules to be delivered. The physical properties of the material used, its degree of crosslinking, and its thickness will determine the time necessary for the molecules to diffuse through the cap material. If diffusion out of the release system is limiting, the cap material delays the onset of release. If diffusion through the cap material is limiting, the cap material determines the release rate of the molecules in addition to delaying the onset of release.

In the active timed release devices, the reservoir caps consist of a thin film of conductive material that is deposited over the reservoir, patterned to a desired geometry, and serves as an anode. Cathodes are also fabricated on the device with their size and placement dependent on the device's application and method of electric potential control. The anode is defined as the electrode where oxidation occurs. Any conductive material capable of dissolving into solution or forming soluble ions or oxidation compounds upon application of an electric potential can be used for the fabrication of the anodes and cathodes. In addition, materials that normally form insoluble ions or oxidation products in response to an electric potential can be used if, for example, local pH changes near the anode cause these oxidation products to become soluble. Examples of suitable reservoir cap materials include metals such as copper, gold, silver, and zinc, and some polymers, as described, for example, by I.C.

Kwon *et al.*, "Electrically erodible polymer gel for controlled release of drugs", *Nature,* **1991**, 354, 291-93; and Y.H. Bae *et al.*, "Pulsatile drug release by electric stimulus", *ACS Symposium Series,* **1994**, 545, 98-110.

Device packaging, control circuitry, and power source

Microelectronic device packages are typically made of an insulating or dielectric material such as aluminum oxide or silicon nitride. Their purpose is to allow all components of the device to be placed in close proximity and to facilitate the interconnection of components to power sources and to each other. For *in vivo* applications of the delivery device, the entire package, including all components (i.e. the device, the microprocessor, and the power source), are coated or encapsulated in a biocompatible material such as poly(ethylene glycol) or polytetrafluoroethylene-like materials. The materials requirements for *in vitro* applications may be less stringent and depend on the particular situation.

The control circuitry consists of a timer, a demultiplexer, a microprocessor, and a input source, for example, a memory source, a signal receiver, or a biosensor. The timer and demultiplexer circuitry can be designed and incorporated directly onto the surface of the microchip during electrode fabrication. The criteria for selection of a microprocessor are small size, low power requirement, and the ability to translate the output from memory sources, signal receivers, or biosensors into an address for the direction of power through the demultiplexer to a specific reservoir on the delivery device. Selection of a source of input to the microprocessor such as memory sources, signal receivers, or biosensors depends on the delivery device's particular application and whether device operation is preprogrammed, controlled by remote means, or controlled by feedback from its environment (i.e. biofeedback).

The criteria for selection of a power source are small size, sufficient power capacity, ability to be integrated into the control circuitry, the ability to be recharged, and the length of time before recharging is necessary. Several lithium-based, rechargeable

microbatteries have been described by S.D. Jones and J.R. Akridge, "Development and performance of a rechargeable thin-film solid-state microbattery", *Journal of Power Sources,* **1995**, 54, 63-67; and J.B. Bates *et al.*, "New amorphous thin-film lithium electrolyte and rechargeable microbattery", *IEEE 35th International Power Sources Symposium,* **1992**, 337-39. These batteries are typically only ten microns thick and occupy 1 cm^2 of area. One or more of these batteries can be incorporated directly onto the delivery device.

METHODS OF DEVICE FABRICATION

Fabrication of the reservoirs

Devices are manufactured using methods known to those skilled in the art, reviewed, for example, by Wolf *et al.* (1986); and Jaeger (1988); Kwon *et al.* (1991).

In a preferred method of microchip manufacture, depicted in Figures 1 and 2, passive and active devices, respectively, fabrication begins by depositing and photolithographically patterning a material, typically an insulating or dielectric material, onto the substrate to serve as an etch mask during reservoir etching. Typical insulating materials for use as a mask include silicon nitride, silicon dioxide, and some polymers, such as polyimide. In a preferred embodiment, a thin film (approximately 1000-3000 Å) of amorphous silicon nitride (SiN_X) is deposited on both sides of a silicon wafer 30/300 by Plasma Enhanced Chemical Vapor Deposition (PECVD). Alternatively, a low stress, silicon-rich nitride can be deposited in a Vertical Tube Reactor (VTR), or a stoichiometric, polycrystalline nitride can be deposited by Low Pressure Chemical Vapor Deposition (LPCVD). Reservoirs are patterned into the silicon nitride film on one side of the wafer 32/320 by ultraviolet photolithography and either plasma etching or a chemical etch consisting of hot phosphoric acid. The patterned silicon nitride serves as an etch mask for the chemical etching of the exposed silicon 34/340 by a concentrated potassium hydroxide solution (approximately 38.5% wt. at a temperature of 80-85°C). Alternatively, the reservoirs can be etched into the substrate

by dry etching techniques such as reactive ion etching or ion beam etching. These techniques are commonly used in the fabrication of microelectronic devices, as reviewed, for example, by Wolf *et al.* (1986) and Jaeger (1988). Use of these microfabrication techniques allows the incorporation of hundreds to thousands of reservoirs on a single microchip. In a passive device, the reservoirs may be as little as one μm apart. In an active device, the distance between the reservoirs may be slightly larger (approximately 10-15 μm) due to the space occupied by the electrodes on or near each reservoir. Reservoirs can be made in nearly any shape and depth, and need not pass completely through the substrate. In a preferred embodiment, the reservoirs etched into a (100) silicon substrate by potassium hydroxide are in the shape of a square pyramid having side walls sloped at 54° and pass completely through the substrate (approximately 300 μm) to the silicon nitride film on the other side of the substrate, forming a SiN_4 membrane. (Here, the silicon nitride film serves as a potassium hydroxide etch stop.) The pyramidal shape allows easy filling of the reservoirs through the large opening of the reservoir (approximately 500 μm by 500 μm) on the patterned side of the substrate, release through the small opening of the reservoir (approximately 30 μm by 30 μm) on the other side of the substrate, and provides a large cavity inside the device for storing the drugs or other molecules to be delivered.

Fabrication of passive timed release reservoir caps

In the fabrication of passive timed release microchips, the reservoir cap material is injected with a micro-syringe 36a, printed with an inkjet printer cartridge, or spin coated 36b into a reservoir having the thin film of insulating mask material still present over the small opening of the reservoir. If injection or inkjet printing methods are used, cap formation is complete after the material is injected or printed into the reservoir 38a and does not require further processing. If spin coating is used, the cap material is planarized by multiple spin coatings 36b. The surface of the film is then etched by a plasma, an ion beam, or chemical etchant until the desired cap thickness is obtained 38b. In a preferred

embodiment, the insulating material used is silicon nitride and the cap material is printed into the reservoir with an inkget cartridge filled with a solution of the cap material.

Reservoir caps control the time at which molecules are released from the reservoirs. Each reservoir cap can be of a different thickness or have different physical properties to vary the time at which each release system containing the molecules is exposed to the surrounding fluids. Injection, inkjet printing, and spin coating are the preferred methods of reservoir filling and any of these methods may be used to fill reservoirs, regardless of the reservoir's shape or size. However, injection and inkjet printing are the preferred methods of filling deep (greater than 10 μm) reservoirs or reservoirs with large openings (greater than 100 μm). For example, to obtain different cap thicknesses using injection, different amounts of cap material are injected or printed directly into each individual reservoir. Spin coating is the preferred method of filling shallow (less than 10 μm) reservoirs, reservoirs that do not pass completely through the substrate, or reservoirs with small (less than 100 μm) openings. Variation in cap thickness or material by spin coating can be achieved by a repeated, step-wise process of spin coating, masking selected reservoirs, and etching. For example, to vary cap thickness with spin coating, the cap material is spin coated over the entire substrate. Spin coating is repeated, if necessary, until the material is nearly planarized. A mask material such as photoresist is patterned to cover the cap material in all the reservoirs except one. Plasma, ion beam, or chemical etchant are used to etch the cap material in the exposed reservoir to the desired thickness. The photoresist is then removed from the substrate. The process is repeated as a new layer of photoresist is deposited and patterned to cover the cap material in all the reservoirs except one (the exposed reservoir is not the same one already etched to its desired thickness). Etching of the exposed cap material in this reservoir continues until the desired cap thickness is obtained. This process of depositing and patterning a mask material such as photoresist, etching,

and mask removal can be repeated until each reservoir has its own unique cap thickness. The techniques, UV photolithography, plasma or ion beam etching, etc., are well known to those skilled in the field of microfabrication.

Although injection, inkjet printing and spin coating are the preferred methods of cap fabrication, it is understood that each reservoir can be capped individually by capillary action, by pulling or pushing the material into the reservoir using a vacuum or other pressure gradient, by melting the material into the reservoir, by centrifugation and related processes, by manually packing solids into the reservoir, or by any combination of these or similar reservoir filling techniques.

Once a cap fabrication method is selected, additional methods for controlling the time of release of molecules from a reservoir can be utilized. Two non-limiting examples include either UV polymerizable polymers or the layering of release system and cap materials. First, if the reservoir caps are made of either an injected, inkjet printed or spin coated UV polymerizable polymer, each cap can be exposed to a different intensity of UV light to give varying degrees of crosslinking and therefore, different degradation or dissolution rates for degradable caps or different permeabilities to the molecules for non-degradable caps. Second, layers of cap material, both degradable and non-degradable, can be inserted between layers of the release system containing the molecules to be delivered by injection, inkjet printing, spin coating, or selective crosslinking. These and other similar methods allow complex release profiles (i.e. pulsatile delivery at irregular time intervals) to be achieved from a single reservoir.

If desired, a passive timed release device can be fabricated without reservoir caps. The rate of release of the molecules is thus solely controlled by the physical and material properties of the release system containing the molecule to be delivered.

Fabrication of active timed release reservoir caps

In a preferred embodiment, photoresist is patterned in the form of electrodes on the surface of the substrate having the reservoirs covered by the thin membrane of insulating or dielectric material. The photoresist is developed such that the area directly over the covered opening of the reservoir is left uncovered by photoresist and is in the shape of an anode. A thin film of conductive material capable of dissolving into solution or forming soluble ions or oxidation compounds upon the application of an electric potential is deposited over the entire surface using deposition techniques such as chemical vapor deposition, electron or ion beam evaporation, sputtering, spin coating, and other techniques known in the art. Exemplary materials include metals such as copper, gold, silver, and zinc and some polymers, as disclosed by Kwon *et al.* (1991) and Bae *et al.* (1994). After film deposition, the photoresist is stripped from the substrate. This removes the deposited film, except in those areas not covered by photoresist (lift-off technique). This leaves conducting material on the surface of the substrate in the form of electrodes 360. An alternative method involves depositing the conductive material over the entire surface of the device, patterning photoresist on top of the conductive film using UV or infrared (IR) photolithography, so that the photoresist lies over the reservoirs in the shape of anodes, and etching the unmasked conductive material using plasma, ion beam, or chemical etching techniques. The photoresist is then stripped, leaving conductive film anodes covering the reservoirs. Typical film thicknesses of the conductive material may range from 0.05 to several microns. The anode serves as the reservoir cap and the placement of the cathodes on the device is dependent upon the device's application and method of electric potential control.

An insulating or dielectric material such as silicon oxide (SiO_x) or silicon nitride (SiN_x) is deposited over the entire surface of the device by methods such as chemical vapor deposition (CVD), electron or ion beam evaporation, sputtering, or spin coating. Photoresist is patterned on top

of the dielectric to protect it from etching except on the cathodes and the portions of the anodes directly over each reservoir 380. The dielectric material can be etched by plasma, ion beam, or chemical etching techniques. The purpose of this film is to protect the electrodes from corrosion, degradation, or dissolution in all areas where electrode film is not necessary for release.

The electrodes are positioned in such a way that when an electric between an anode and a cathode, the unprotected (not covered by dielectric) portion of the anode reservoir cap oxidizes to form soluble compounds or ions that dissolves into solution, exposing the release system containing the molecules to the surrounding fluids. The molecules are released from the reservoir at a rate dependent upon the degradation or dissolution rate of a degradable release system or the rate of diffusion of the molecules out of or through a non-degradable release system.

Removal of the insulator membrane (reservoir etch stop)

The thin membrane of insulating or dielectric material covering the reservoir used as a mask and an etch stop during reservoir fabrication must be removed from the active timed release device before filling reservoir 400 and from the passive timed release device (if the reservoir extends completely through the substrate) after filling reservoir 44. The film may be removed in two ways. First, the film can be removed by an ion beam or reactive ion plasma. In a preferred embodiment, the silicon nitride film used as the insulating material can be removed by a reactive ion plasma composed of oxygen and fluorine containing gases such as CHF_3 or CF_4. Second, the film can be removed by chemical etching. For example, buffered hydrofluoric acid (BHF or BOE) can be used to etch silicon dioxide and hot phosphoric acid can be used to etch silicon nitride.

Reservoir filling

The release system containing the molecules for delivery is inserted into the large opening of the reservoir by injection, inkjet printing or spin coating 40a/40b/400. Each reservoir can contain a different molecule and dosage. Similarly, the release kinetics of the molecule in each reservoir can be varied by the choice of the release system and cap materials. In addition, the mixing or layering of release system and cap materials in each reservoir can be used to tailor the release kinetics to the needs of a particular application.

The distribution over the microchip of reservoirs filled with the release system containing the molecules to be delivered can vary depending on the medical needs of the patient or other requirements of the system. For applications in drug delivery, for example, the drugs in each of the rows can differ from each other. One row may contain a hormone and another row may contain a metabolite. Also, the release system can differ within each row to release a drug at a high rate from one reservoir and a slow rate from another reservoir. The dosages can also vary within each row. For those devices having deep (greater than 10 μm) reservoirs or reservoirs with large (greater than 100 μm) openings, differences in reservoir loading can be achieved by injection or inkjet printing of different amounts of material directly into each reservoir. Variation between reservoirs is achieved in devices having shallow (less than 10 μm) reservoirs, reservoirs that do not pass completely through the substrate, or reservoirs with small (less than 100 μm) openings by a repeated, step-wise process of masking selected reservoirs, spin coating, and etching, as described above regarding the fabrication by spin coating of passive timed release reservoir caps. Preferably, the release system and molecules to be delivered are mixed before application to the reservoirs. Although injection, inkjet printing and spin coating are the preferred methods of filling reservoirs, it is understood that each reservoir can be filled individually by capillary action, by pulling or pushing the material into the reservoir using a vacuum or other pressure gradient, by

melting the material into the reservoir, by centrifugation and related processes, by manually packing solids into the reservoir, or by any combination of these or similar reservoir filling techniques.

Device packaging, control circuitry, and power source

The openings through which the reservoirs of passive and active devices are filled are sealed by wafer bonding or with a waterproof epoxy or other appropriate material impervious to the surrounding fluids 44/440. For *in vitro* applications, the entire unit, except for the face of the device containing the reservoirs and electrodes, is encased in a material appropriate for the system. For *in vivo* applications, the unit would be encapsulated in a biocompatible material such as poly(ethylene glycol) or polytetrafluoroethylene.

The mechanism for release of molecules by the active timed release device does not depend on multiple parts fitted or glued together which must retract or dislodge. Control of the time of release of each reservoir can be achieved by a preprogrammed microprocessor, by remote control, by a signal from a biosensor, or by any combination of these methods, as shown schematically in Figure 3. First, a microprocessor is used in conjunction with a source of memory such as programmable read only memory (PROM), a timer, a demultiplexer, and a power source such as a microbattery, such as is described, for example, by Jones *et al.* (1995) and Bates *et al.* (1992). The release pattern is written directly into the PROM by the user. The PROM sends these instructions to the microprocessor. When the time for release has been reached as indicated by the timer, the microprocessor sends a signal corresponding to the address (location) of a particular reservoir to the demultiplexer. The demultiplexer sends an input, such as an electric potential, to the reservoir addressed by the microprocessor. A microbattery provides the power to operate the PROM, timer, and microprocessor, and provides the electric potential input that is directed to a particular reservoir by the demultiplexer. The manufacture, size, and location of each of these components is dependent upon the requirements of a particular

application. In a preferred embodiment, the memory, timer, microprocessor, and demultiplexer circuitry is integrated directly onto the surface of the chip. The microbattery is attached to the other side of the chip and is connected to the device circuitry by vias or thin wires. However, in some cases, it is possible to use separate, prefabricated, component chips for memory, timing, processing, and demultiplexing. These are attached to the backside of the miniaturized delivery device with the battery. The size and type of prefabricated chips used depends on the overall dimensions of the delivery device and the number of reservoirs. Second, activation of a particular reservoir by the application of an electric potential can be controlled externally by remote control. Much of the circuitry used for remote control is the same as that used in the preprogrammed method. The main difference is that the PROM is replaced by a signal receiver. A signal such as radio waves, low power laser, or ultrasound is sent to the receiver by an external source, for example, computers or ultrasound generators. The signal is sent to the microprocessor where it is translated into a reservoir address. Power is then directed through the demultiplexer to the reservoir having the appropriate address. Third, a biosensor is integrated into the microchip to detect molecules in the surrounding fluids. When the concentration of the molecules reaches a certain level, the sensor sends a signal to the microprocessor to activate one or more reservoirs. The microprocessor directs power through the demultiplexer to the particular reservoir(s).

Electric Potential Control Methods

The reservoir caps of an active device are anodes that oxidize to form soluble compounds and ions when a potential is applied between the anode and a cathode. For a given electrode material and electrolyte, there exists a range of electric potentials over which these oxidation reactions are thermodynamically and kinetically favorable. In order to reproducibly oxidize and open the device's reservoir caps, the anode potential must be maintained in this potential range.

There exist two primary control methods for maintaining an electrode within a specific potential range. The first method is called potentiostatic control. As the name indicates, the potential is kept constant during reservoir activation. Control of the potential is typically accomplished by incorporating a third electrode into the system that has a known, constant potential, called a reference electrode. The reference electrode can take the form of an external probe whose tip is placed within one to three mm of the anode surface. The potential of the anode is measured and controlled with respect to the known potential of a reference electrode such as a saturated calomel electrode (SCE). In a preferred embodiment of potentiostatic control, a thin film reference electrode and potential feedback controller circuitry could be fabricated directly onto the surface of the microchip. For example, a microfabricated Ag/AgCl reference electrode integrated with a microchip device would enable the device to maintain the anode potential of an activated reservoic within the oxidation regime until the reservoir was completely opened. The second method is called galvanostatic control. As the name indicates, the current is kept constant during reservoir activation. One drawback to this method of control is that there is more than one stable potential for a given current density. However, if the current density versus potential behavior is well characterized for the microchip device in a particular electrolyte system, the current density that will maintain the anode in teh oxidation regime will be known. In this case, the galvanostatic method of potential control would be preferable to the potentiostatic control, because galvanostatic control does not require a reference electrode.

MICROCHIP APPLICATIONS

Passive and active microchip devices have numerous *in vitro* and *in vivo* applications. The microchip can be used *in vitro* to deliver small, controlled amounts of chemical reagents or other molecules to solutions or reaction mixtures at precisely controlled times and rates. Analytical chemistry and medical diagnostics are examples of fields where the

microchip delivery device can be used. The microchip can be used *in vivo* as a drug delivery device. The microchips can be implanted into a patient, either by surgical techniques or by injection, or can be swallowed. The microchips provide delivery of drugs to animals or persons who are unable to remember or be ambulatory enough to take medication. The microchips further provide delivery of many different drugs at varying rates and at varying times of delivery.

The present invention will be further understood by reference to the following non-limiting examples.

Example 1: Microchip with passive timed drug release.

A passive timed release device, microchip 10 is shown in Figure 4. Microchip 10 is formed from substrate 14. Reservoirs 16 are etched into substrate 14. Positioned in reservoirs 16 is a release system containing molecules 18 for delivery. The reservoirs are capped with reservoir caps 12. The release system and the molecules for delivery 18 can vary between rows 20a, 20b, 20c, and within reservoirs of each row.

Microchip 10 can be inserted into solution for *in vitro* applications or be implanted in a selected part of the body or swallowed for *in vivo* applications and left to operate without requiring further attention. When exposed to the surrounding fluids, reservoir caps 12 will degrade, dissolve or become permeable to the release system containing molecules for delivery 18.

Figures 7a-i depict several additional possible configurations for passive delivery devices.

Example 2: Microchip with active controlled time release.

A drug delivery device that provides active timed release is shown as microchip 100 in Figure 5. Microchip 100 is similar to microchip 10 except that microchip 100 contains electrodes that provide for active timed release. Microchip 100 is formed from substrate 160, release system containing molecules 180 for delivery, anode reservoir caps 120, and cathodes 140. Preferably, microchip 100 further includes an input source, a microprocessor, a timer, a demultiplexer, and a power source

(not shown). The power source provides energy to drive the reaction between selected anodes and cathodes. Upon application of a small potential between an anode and cathode, electrons pass from the anode to the cathode through the external circuit causing the anode material to oxidize and form soluble compounds or ions that dissolve into the surrounding fluids, exposing the release system containing the molecules for delivery 180 to the surrounding fluids. The microprocessor directs power to specific electrode pairs through a demultiplexer as directed by a PROM, remote control, or biosensor.

Figure 6 is a schematic of a second embodiment of a microchip 200 from from substrate 260 actively releasing drug 280 from the device upon application of an electric potential between an anode and cathode, which, unlike the device in Figure 5, includes an insulator overlayer.

Figures 8a-c depicts three additional possible configurations for active delivery devices.

We claim:

1. A microchip device for the release of molecules comprising

a substrate, and

a plurality of reservoirs in the substrate, wherein the reservoirs controllably release molecules incorporated therein.

2. The device of claim 1 wherein the reservoirs comprise different types of molecules, different amounts of molecules, or combinations thereof.

3. The device of claim 1 wherein release of the molecules is controlled by a release system incorporating the molecules in the reservoir.

4. The device of claim 3 further comprising degradable reservoir caps positioned on the reservoirs over the release system, wherein the degradation rate of the cap determines the time at which the molecules are released from the reservoir.

5. The device of claim 4 wherein the reservoir caps have different thicknesses.

6. The device of claim 4 wherein the release system in a reservoir degrades or dissolves to release the molecules after the reservoir cap is degraded or dissolved.

7. The device of claim 4 wherein pulsatile release is obtained from a single reservoir by layering different release system and reservoir cap materials in the reservoir.

8. The device of claim 4 wherein the release system is non-degradable, and diffusion of the molecules out of the release system provides a pulsed release of the molecules after the degradation of the reservoir cap.

9. The device of claim 3 comprising non-degradable reservoir caps positioned on the reservoirs over the release system, wherein the rate of diffusion of the molecules through the cap determines the time at which the molecules are released from the reservoirs.

10. The device of claim 4 further comprising cathodes, a microprocessor, a timer, a demultiplexer, and a power source, wherein the reservoir caps are anodes and are each surrounded by one of the cathodes, wherein upon application of an electric potential between each cathode and anode, the reservoir cap oxidizes, dissolves in solution, and exposes the underlying release system to the surrounding fluids.

11. The device of claim 10 wherein the microprocessor function is directed by a source of memory preprogrammed to activate the electrodes of individual reservoirs at specific times.

12. The device of claim 10 wherein the microprocessor function is directed by remote control to activate the electrodes of each reservoir.

13. The device of claim 10 further comprising a biosensor, wherein the microprocessor function is directed by the biosensor to activate the electrodes of each reservoir.

14. The device of claim 2 wherein the release system comprises drug molecules in an excipient or diluent.

15. The device of claim 14 wherein the release system in each reservoir is formed of the molecules to be released, wherein the dissolution rate of the molecules determines the rate of release of the molecules.

16. A method of fabricating a device for the release of molecules comprising:

providing a substrate;

depositing and patterning an insulating material on the substrate for use as an etch mask;

etching a plurality of reservoirs in the substrate;

filling the reservoirs with release system and cap materials; and

etching release system and cap materials.

17. The method of claim 16 further comprising removing a thin film of insulating material over the reservoirs.

18. The method of claim 16 further comprising filling each reservoir with different types and amounts of cap materials and release systems containing molecules to be delivered.

19. The method of claim 16 wherein the reservoirs are filled by injection, inkjet printing or spin coating.

20. The method of claim 19 wherein the reservoirs are filled by inkjet printing.

21. The method of claim 17 further comprising depositing a thin film of conductive material over the thin film of insulating material over each reservoir.

22. The method of claim 21 further comprising patterning the conductive film into electrodes so that an anode covers each reservoir opening and a cathode surrounds each anode.

23. The method of claim 22 further comprising depositing a material over each electrode, except the anode directly over the reservoir and the cathode surrounding the exposed portion of the anode.

24. A method for the delivery of molecules comprising

providing at a site where the molecules are to be delivered a microchip device for the release of molecules comprising a substrate, and a plurality of reservoirs in the substrate, wherein the reservoirs controllably release molecules incorporated therein.

25. The method of claim 24 wherein the molecules are drugs, comprising administering, implanting or injecting the microchip into a patient.

26. The method of claim 25 wherein the molecules are a drug selected from the group consisting of nucleic acids, proteins, amino acids, polysaccharides, and organic or synthetic molecules.

27. The method of claim 26 wherein the drugs are in combination with a pharmaceutically acceptable carrier.

28. The method of claim 24 wherein the molecules are diagnostic or chemical reagents.

29. The method of claim 24 wherein the molecules are released in a pulsatile or continuous manner.

30. The method of claim 24 wherein the release system is formed by the molecules to be released.

31. The method of claim 24 wherein degradable reservoir caps are positioned on the reservoirs over the release system, wherein the degradation, dissolution or diffusion rate of the cap determines the time at which the molecules are released from the reservoir.

32. The method of claim 24 wherein the device further comprises cathodes, a microprocessor, a timer, a demultiplexer, and a power source, wherein the reservoir caps are anodes and are each surrounded by one of the cathodes, wherein the method further comprises applying an electric potential between each cathode and anode, to oxidize the reservoir cap and expose the underlying release system to the surrounding fluids.

33. The method of claim 32 wherein the microprocessor function is directed by a source of memory preprogrammed to activate the electrodes of individual reservoirs at specific times, wherein the method further comprises programming the memory.

34. The method of claim 32 wherein the microprocessor function is directed by remote control to activate the electrodes of each reservoir.

35. The method of claim 32 wherein the device further comprises a biosensor, wherein the microprocessor function is directed by the biosensor to activate the electrodes of each reservoir.

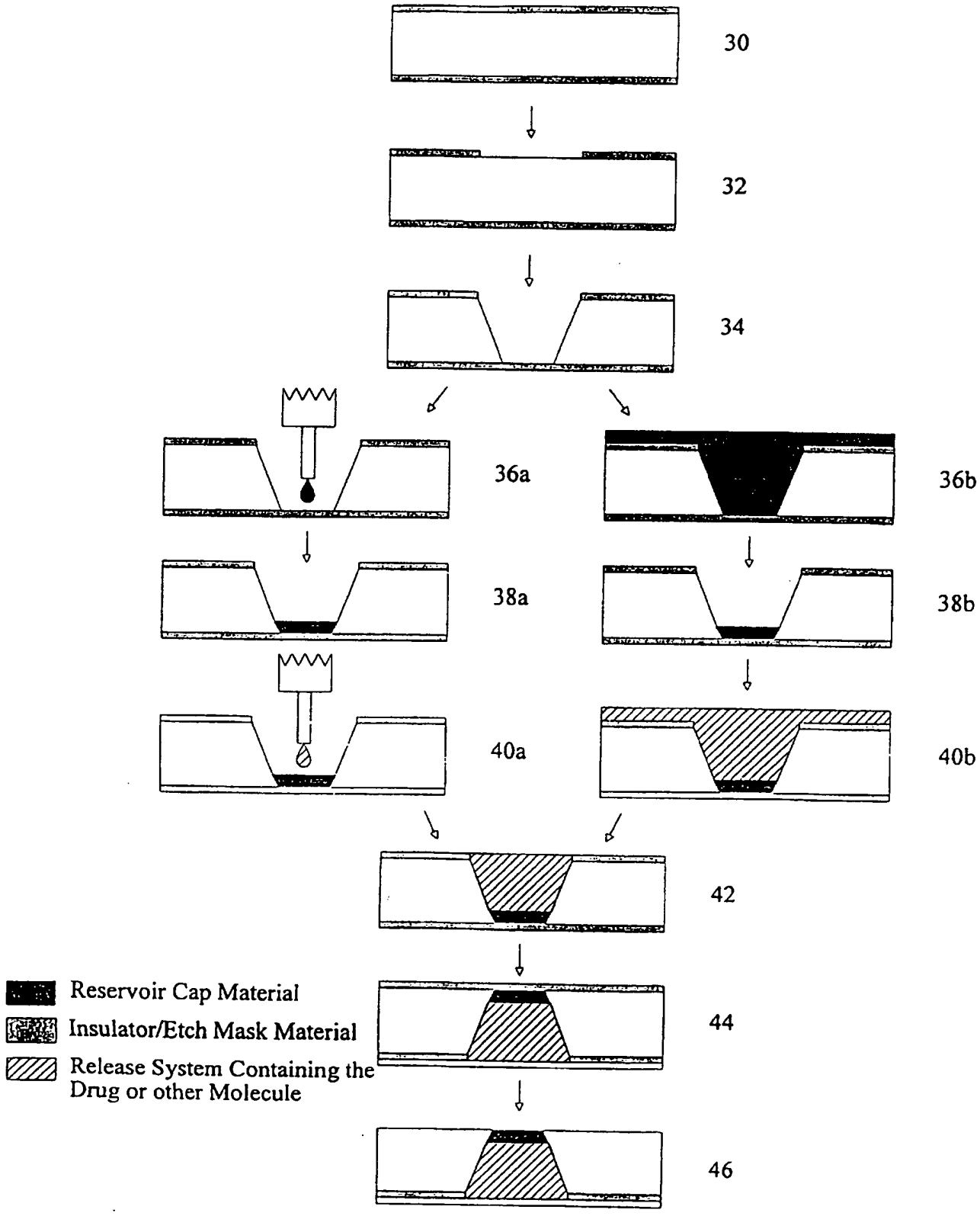


Figure 1. Fabrication of a Passive Device

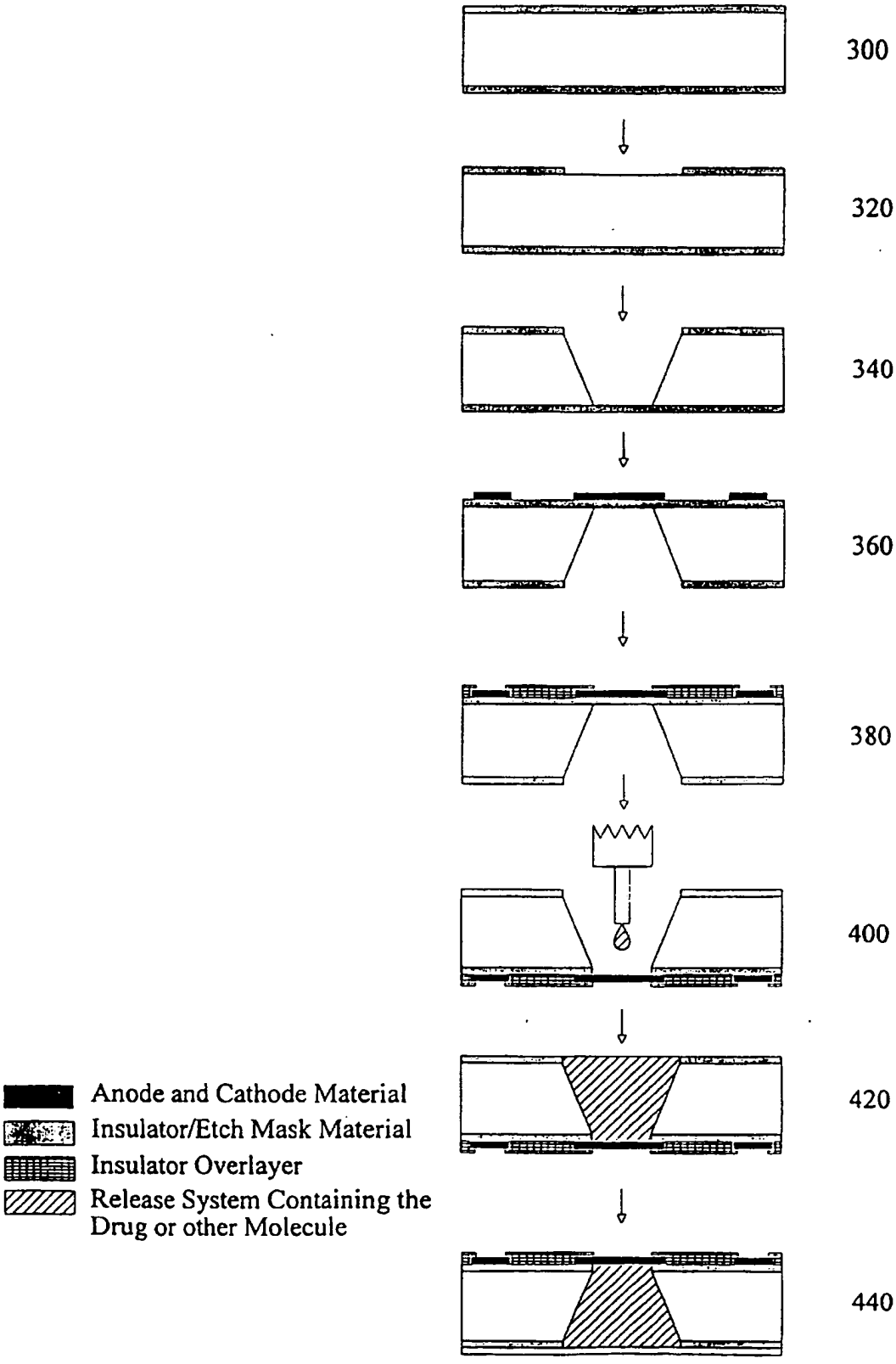


Figure 2. Fabrication of an Active Device

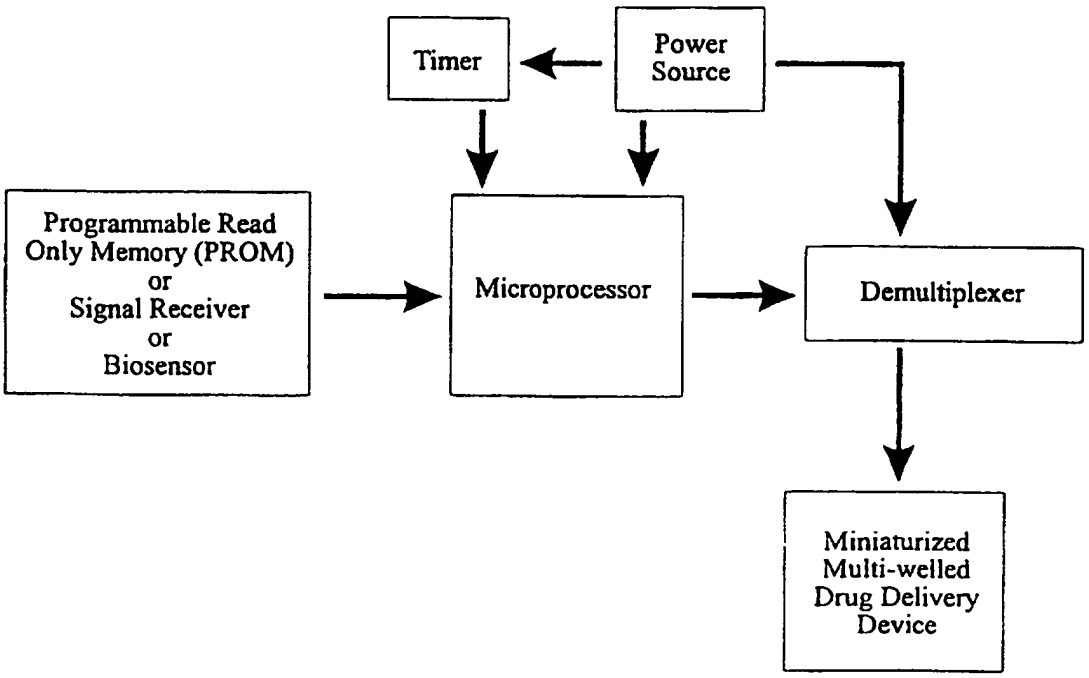


Figure 3. Flowsheet of Device Control Circuitry

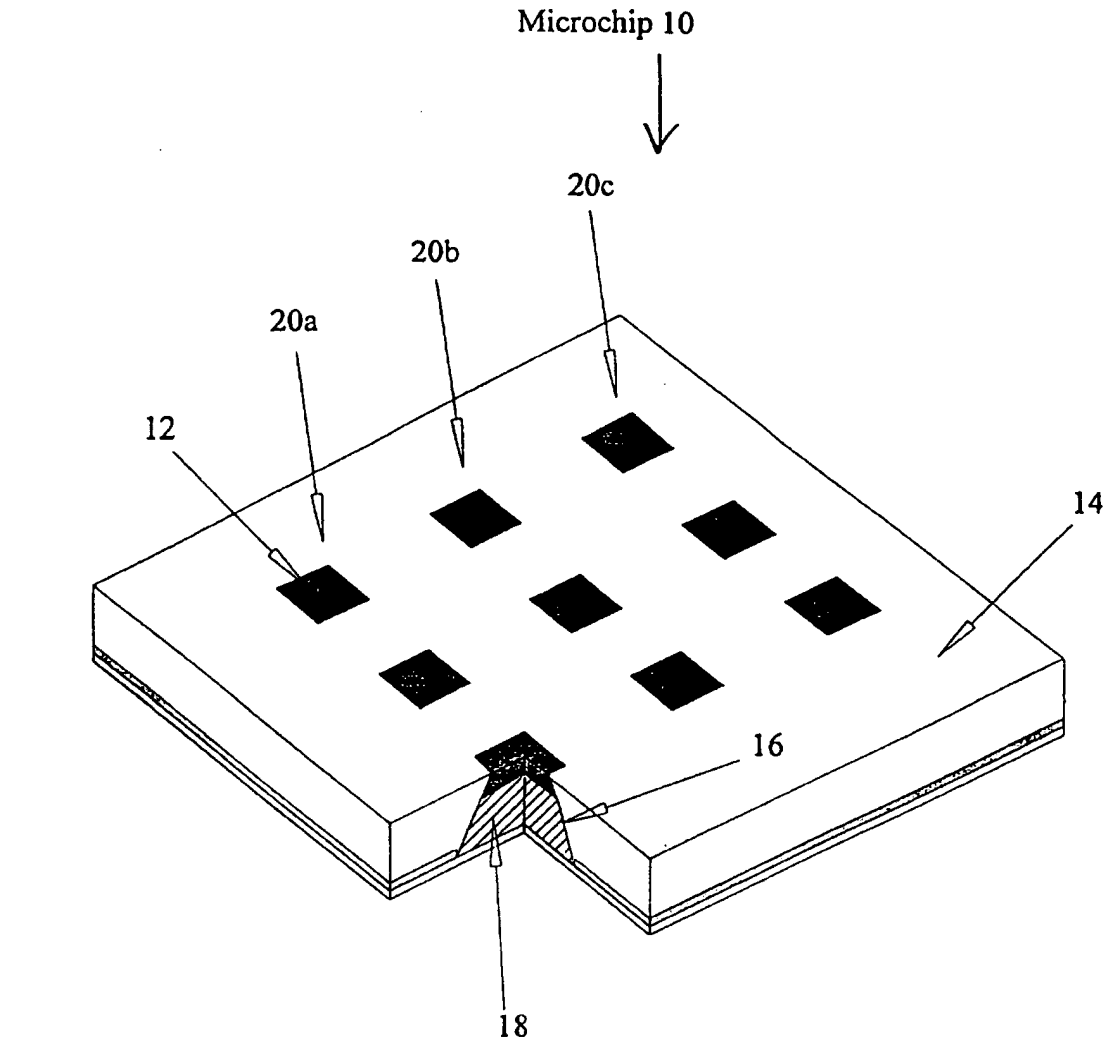
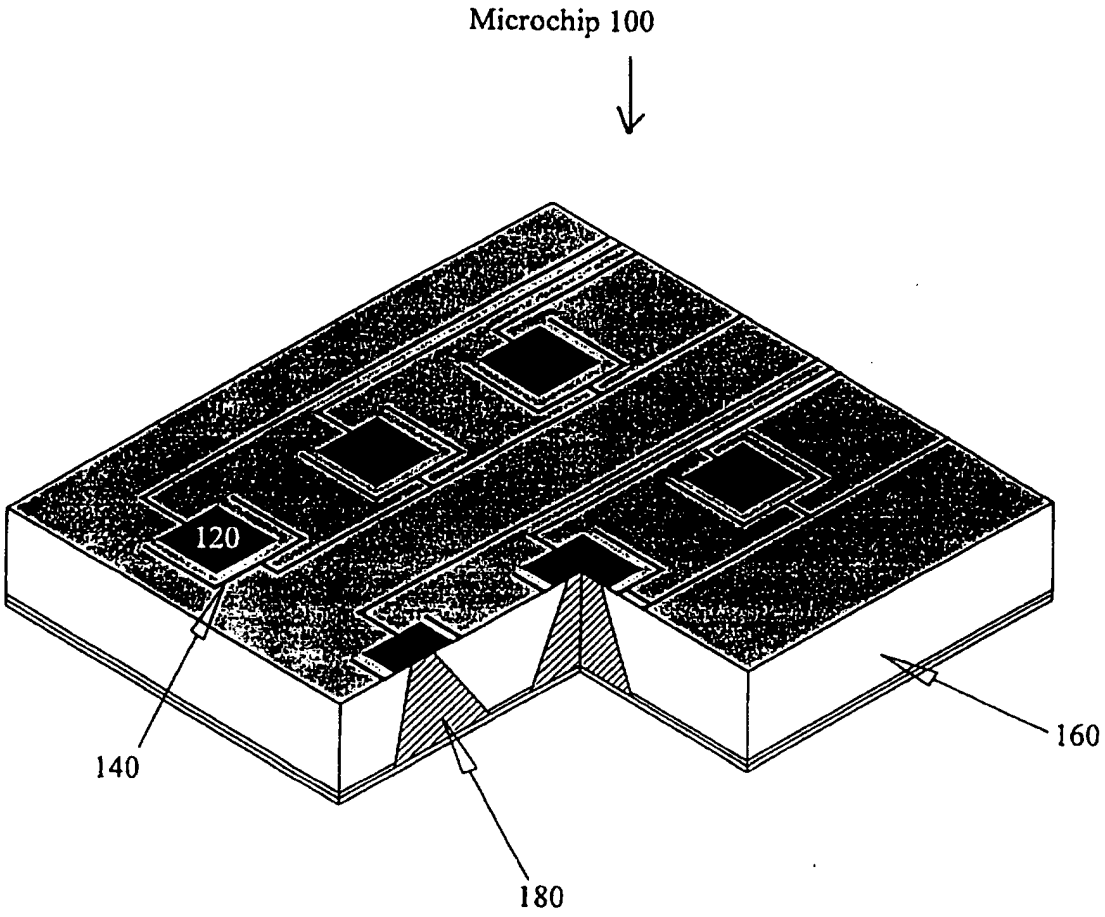


Figure 4. Schematic of a Passive Device



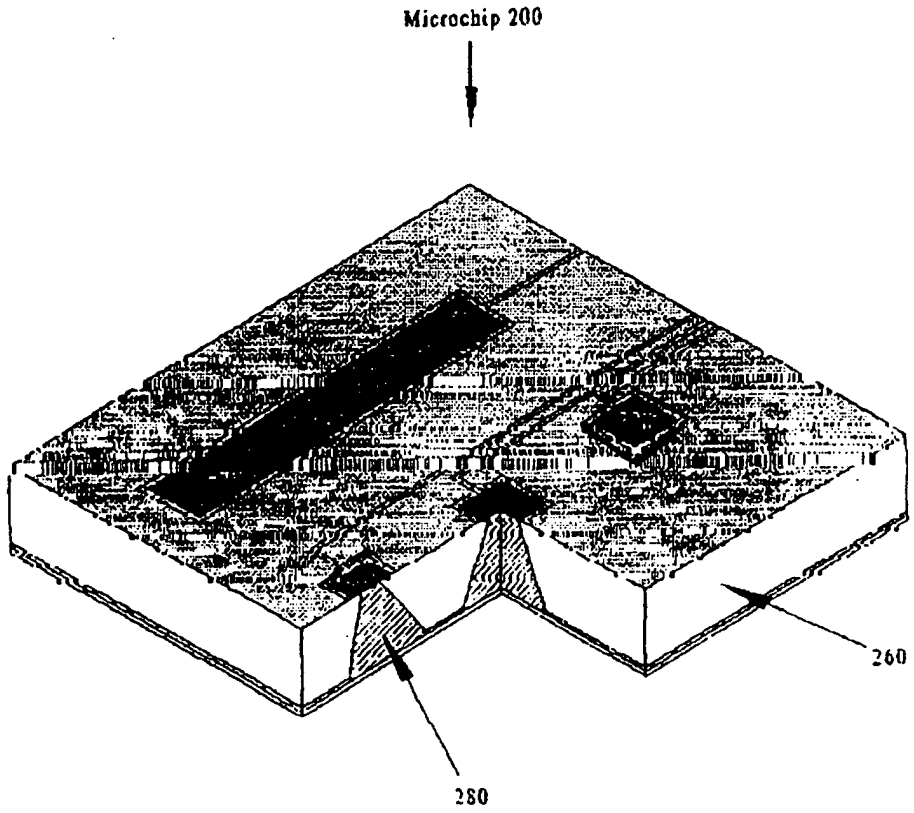
Release System Containing the Drug or other Molecule

Anode and Cathode Material

Insulator/Etch Mask Material

Figure 5. Schematic of an Active Device

(not including insulator overlayer)



Release System Containing the Drug or other Molecule

Anode and Cathode Material

Insulator Overlayer & Etch Mask Material

Figure 6. Schematic of an Active Device

(including insulator overlayer)

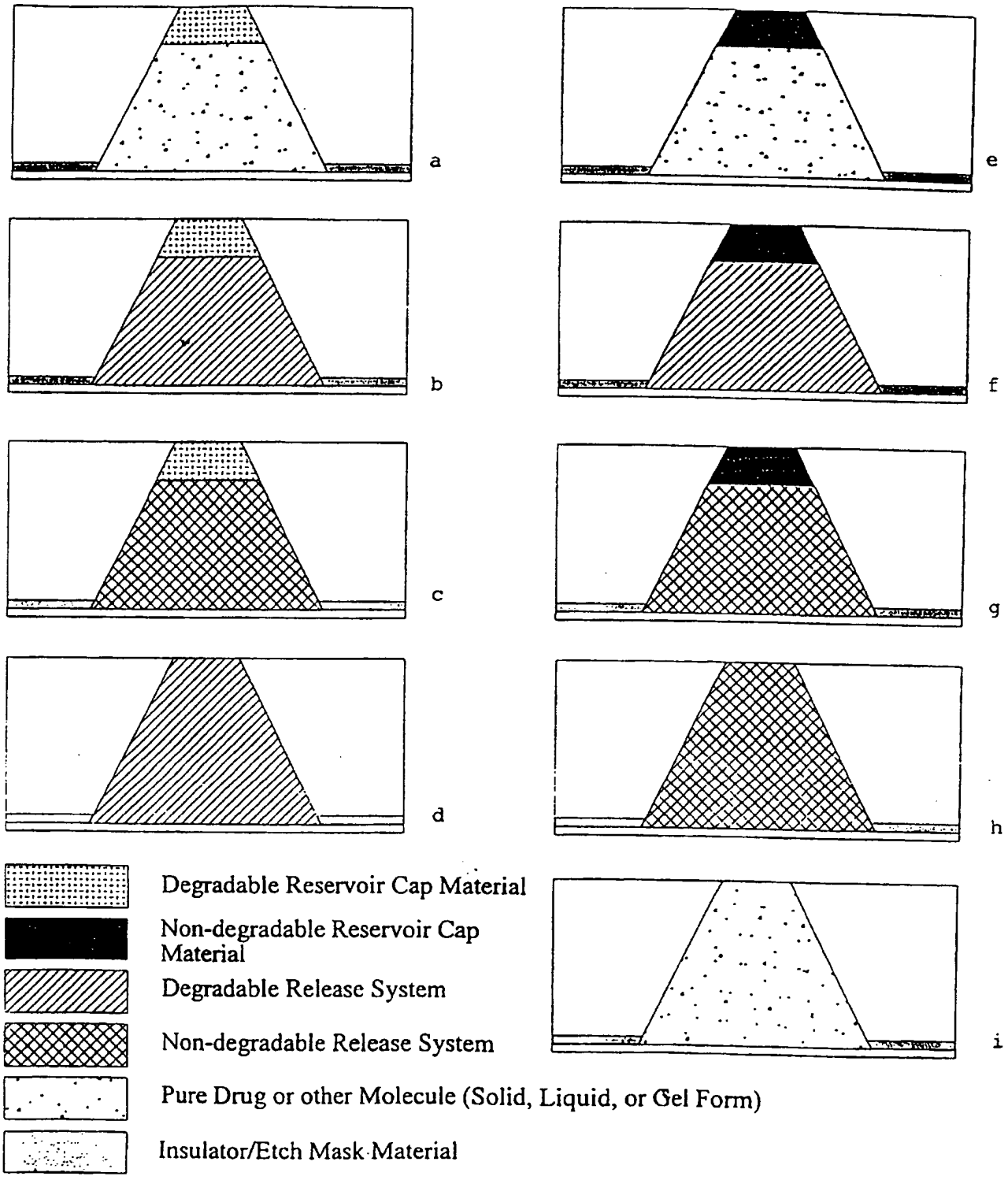
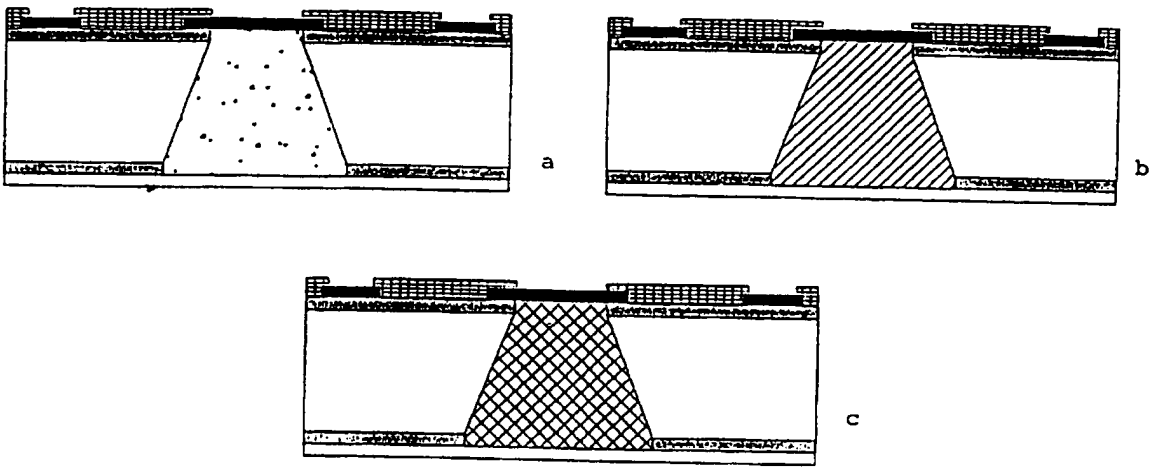


Figure 7. Several Possible Configrations for Passive Delivery Devices



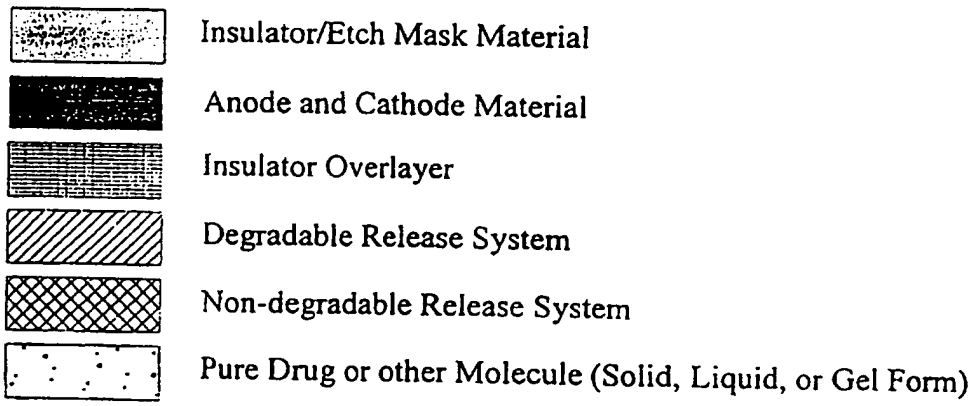


Figure 8. Several Possible Configrations for Active Delivery Devices

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(57) Abstract

Microchips are provided, which control both the rate and time of release of multiple chemical substances and which allow for the release of a wide variety of molecules in either a continuous or pulsatile manner. In all of the preferred embodiments, a material that is impermeable to the drugs or other molecules to be delivered and the surrounding fluids is used as the substrate. Reservoirs are etched into the substrate using either chemical (wet) etching or ion beam (dry) etching techniques well-known in the field of microfabrication. Hundreds to thousands of reservoirs can be fabricated on a single microchip using these techniques. A release system, which includes the molecules to be delivered, is inserted into the reservoirs by injection, inkjet printing or spin coating methods. Exemplary release systems include polymers and polymeric matrices, non-polymeric matrices, and other excipients or diluents. The physical properties of the release system control the rate of release of the molecules. The reservoirs can contain multiple drugs or other molecules in variable dosages. The filled reservoirs can be capped with materials that either degrade, dissolve, or allow the molecules to diffuse passively out of the reservoir over time or materials that, upon application of an electric potential, oxidize to form soluble compounds or ions that dissolve into the surrounding fluids. Release from an active device can be controlled by a preprogrammed microprocessor, remote control, or by biosensors.

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MICROCHIP DRUG DELIVERY DEVICES

Background of the Invention

This invention relates to miniaturized drug delivery devices and more particularly, to controlled time and rate release multi-welled drug delivery devices.

Drug delivery is an important aspect of medical treatment. The efficacy of many drugs is directly related to the way in which they are administered. Some therapies require that the drug be repeatedly administered to the patient over a long period of time. This makes the selection of a proper drug delivery method problematic. Patients often forget, are unwilling, or are unable to take their medication. Drug delivery also becomes problematic when the drugs are too potent for systemic delivery. Therefore, attempts have been made to design and fabricate a delivery device which is capable of the controlled, pulsatile or continuous release of a wide variety of molecules including, but not limited to, drugs and other therapeutics.

Controlled release polymeric devices have been designed to provide drug release over a period of time via diffusion of the drug out of the polymer and/or degradation of the polymer over the desired time period following administration to the patient. However, these devices are relatively simple.

U.S. Patent No. 5,490,962 to Cima, et al. discloses the use of three dimensional printing methods to make more complex devices which provide release over a desired time frame, of one or more drugs. Although the general procedure for making a complex device is described, specific designs are not detailed.

U.S. Patent No. 4,003,379 to Ellinwood describes an implantable electromechanically driven device that includes a flexible retractable walled container, which receives medication from a storage area via an inlet and then dispenses the medication into the body via an outlet. U.S. Patent No. 4,146,029 and U.S. Patent No. 3,692,027 to Ellinwood

disclose self-powered medication systems that have programmable miniaturized dispensing means. U.S. Patent No. 4,360,019 to Jassawalla discloses an implantable infusion device that includes an actuating means for delivery of the drug through a catheter. The actuating means includes a solenoid driven miniature pump. All of these devices include miniature power-driven mechanical parts that are required to operate in the body, i.e., they must retract, dispense, or pump. These are complicated and subject to breakdown. Moreover, due to complexity and size restrictions, they are unsuitable to deliver more than a few drugs or drug mixtures at a time.

It is therefore an object of the present invention to provide a simple to use and manufacture, dependable, multi-welled delivery device for drugs and other molecules which can operate for weeks or years at a time.

It is another object of the present invention to provide such a device that allows delivery of drugs or other molecules in either a pulsatile or continuous manner.

It is yet another object of the present invention to provide such a device that allows the delivery to be controlled either passively or actively.

It is also an object of the present invention to provide such a device that can hold many different drugs or other molecules of varying dosages and is small enough to be implanted, injected or swallowed, if desired.

Summary of the Invention

Microchips for delivery of a wide variety of molecules are provided. Microchips are miniaturized devices constructed using methods commonly applied to the manufacture of integrated circuits such as ultraviolet (UV) photolithography, reactive ion etching, and electron beam evaporation. The microchips provide control over the rate the molecules

are released as well as the time at which release begins. The time of release can be controlled passively or actively.

In the preferred embodiments, a material which is impermeable to the surrounding fluids and to the molecules to be delivered is used as the substrate. Examples of substrate materials include ceramics, semiconductors such as silicon, and degradable and non-degradable polymers. Reservoirs are etched into the substrate using either chemical (wet) etching or ion (dry) etching techniques commonly used in microfabrication. Hundreds to thousands of reservoirs can be created in this manner and contained in a single microchip. Typically, a release system containing, encapsulating, or consisting of the molecule to be delivered is inserted into the reservoirs by injection, inkjet printing, or other means. The release system controls the rate of release of the molecule. The rate of release is a function of the composition and structure of the release system. The device design makes it possible to fill the reservoirs with a release system in solid, liquid, or gel form. Each of the reservoirs of a single microchip can contain different molecules and/or different amounts and concentrations, which can be released independently.

In a preferred embodiment, the reservoir cap enables passive timed release, not requiring a power source, of molecules. The reservoirs are capped with materials that degrade or dissolve at a known rate or have a known permeability (diffusion constant) for the molecules to be delivered. Therefore, the degradation, dissolution or diffusion characteristics of the cap material determine the time at which the release of molecules in a particular reservoir begins. In effect, the microchip provides dual control of the release of molecules by selection of the release system (rate controller) and selection of the cap material (time controller, and in some cases, rate controller).

In another preferred embodiment, the reservoir cap enables active timed release, requiring a power source, of molecules. In this embodiment, the reservoir caps consist of a thin film of conductive

material that is deposited over the reservoir, patterned to a desired geometry, and serves as an anode. Cathodes are also fabricated on the device with their size and placement dependent on the device's application and method of electric potential control. Conductive materials capable of dissolving into solution or forming soluble compounds or ions upon the application of an electric potential, including metals such as copper, gold, silver, and zinc and some polymers, are used in the active timed release device. When an electric potential is applied between an anode and cathode, the conductive material of the anode above the reservoir oxidizes to form soluble compounds or ions that dissolve into solution, exposing the release system containing the molecules to be delivered to the surrounding fluids. Alternatively, the application of an electric potential can be used to create changes in local pH near the anode reservoir cap to allow normally insoluble ions or oxidation products to become soluble. This would allow the reservoir to dissolve and expose the release system to the surrounding fluids. In either case, the molecules to be delivered are released into the surrounding fluids by diffusion out of or by degradation or dissolution of the release system. The frequency of release is controlled by incorporation of a miniaturized power source and microprocessor onto the microchip. Activation of any reservoir can be achieved by preprogramming the microprocessor, by remote control, or by a signal from a biosensor.

Description of the Drawings

Figure 1 depicts a typical fabrication scheme for a passive delivery device.

Figure 2 depicts a typical fabrication scheme for an active delivery device.

Figure 3 depicts a typical device control circuitry flowsheet.

Figure 4 depicts a passive delivery device.

Figure 5 depicts an active delivery device.

Figure 6 depicts an active device including insulator overlayers.

Figures 7a-i are schematic views of several configurations of passive delivery devices.

Figures 8a-c are schematic views of several configurations of active delivery devices.

Detailed Description

Microchip devices have been provided which can accurately deliver drugs and other molecules at defined rates and times according to the needs of the patient or other experimental system. As used herein, a "microchip" is a miniaturized device fabricated using methods commonly applied to the manufacture of integrated circuits such as ultraviolet (UV) photolithography, reactive ion etching, and electron beam evaporation, as described, for example, by S. Wolf and R.N. Tauber, *Silicon Processing for the VLSI Era, Volume 1 - Process Technology*, Lattice Press, Sunset Beach, CA, 1986; and R.C. Jaeger, *Introduction to Microelectronic Fabrication*, Volume V in the Modular Series on Solid State Devices, Addison-Wesley, Reading, MA, 1988. The microchips provide control over the rate the molecules are released as well as the time at which release begins. The time of release can be controlled passively or actively. The microchip fabrication procedure allows the manufacture of devices with primary dimensions (length of a side if square or rectangular, or diameter if circular) ranging from a few millimeters to several centimeters. A typical device thickness is 300 μm. However, the thickness of the device can vary from approximately 10 μm to several millimeters. Changing the device thickness affects the maximum number of reservoirs that may be incorporated onto a microchip and the volume of each reservoir. *In vivo* applications of the device would typically require devices having a primary dimension of 2 cm or smaller. Devices for *in vivo* applications are small enough to be swallored or implanted using minimally invasive procedures. Smaller *in vivo* devices (on the order of a millimeter) can be implanted using a catheter or other

injectable means. Devices for *in vitro* applications have fewer size restrictions and, if necessary, can be made much larger than the dimension ranges for *in vivo* devices.

MATERIALS FOR DEVICE FABRICATION

Each device consists of a substrate, reservoirs, and a release system containing, enclosing, or layered with the molecules to be delivered. Devices which control the release time of the molecules may include reservoir caps. Active devices may include control circuitry and a power source.

The substrate

The substrate contains the etched or machined reservoirs and serves as the support for the microchip. Any material which can serve as a support, is suitable for etching or machining, and is impermeable to the molecules to be delivered and to the surrounding fluids, for example, water, blood, electrolytes or other solutions, may be used as a substrate. Biocompatibility of the substrate material is preferred, but not required. For *in vivo* applications, non-biocompatible materials may be encapsulated in a biocompatible material, such as poly(ethylene glycol) or polytetrafluoroethylene-like materials, before use. One example of a strong, non-degradable, easily etched substrate that is impermeable to the molecules to be delivered and the surrounding fluids is silicon. In another embodiment, the substrate is made of a strong material that degrades or dissolves over a period of time into biocompatible components. This embodiment is preferred for *in vivo* applications where the device is implanted and physical removal of the device at a later time is not feasible or recommended, for example, brain implants. An example of a class of strong, biocompatible materials are the poly(anhydride-*co*-imides), discussed by K.E. Uhrich *et al.*, "Synthesis and characterization of degradable poly(anhydride-*co*-imides)", *Macromolecules*, **1995**, 28, 2184-93.

Release system

The molecules to be delivered may be inserted into the reservoirs in their pure form, as a liquid solution or gel, or they may be encapsulated within or by a release system. As used herein, "release system" includes both the situation where the molecules are in pure form, as either a solid or liquid, or are in a matrix formed of degradable material or a material which releases incorporated molecules by diffusion out of or disintegration of the matrix. The molecules can be sometimes contained in a release system because the degradation, dissolution or diffusion properties of the release system provide a method for controlling the release rate of the molecules. The molecules can be homogeneously or heterogeneously distributed within the release system. Selection of the release system is dependent on the desired rate of release of the molecules. Both non-degradable and degradable release systems can be used for delivery of molecules. Suitable release systems include polymers and polymeric matrices, non-polymeric matrices, or inorganic and organic excipients and diluents such as, but not limited to, calcium carbonate and sugar. Release systems may be natural or synthetic, although synthetic release systems are preferred due to the better characterization of release profiles. The release system is selected based on the period over which release is desired, generally in the range of at least three to twelve months for *in vivo* applications. In contrast, release times as short as a few seconds may be desirable for some *in vitro* applications. In some cases, continuous (constant) release from a reservoir may be most useful. In other cases, a pulse (bulk) release from a reservoir may provide more effective results. Note that a single pulse from one reservoir can be transformed into pulsatile release by using multiple reservoirs. It is also possible to incorporate several layers of a release system and other materials into a single reservoir to achieve pulsatile delivery from a single reservoir. Continuous release can be achieved by incorporating a release system that degrades, dissolves, or allows diffusion of molecules through

it over an extended period of time. In addition, continuous release can be stimulated by releasing several pulses of molecules in quick succession.

The release system material can be selected so that molecules of various molecular weights are released from a reservoir by diffusion out or through the material or degradation of the material. Biodegradable polymers, bioerodible hydrogels, and protein delivery systems are preferred for release of molecules by diffusion, degradation, or dissolution. In general, these materials degrade or dissolve either by enzymatic hydrolysis or exposure to water *in vivo* or *in vitro*, or by surface or bulk erosion. Representative synthetic, biodegradable polymers include: poly(amides) such as poly(amino acids) and poly(peptides); poly(esters) such as poly(lactic acid), poly(glycolic acid), poly(lactic-*co*-glycolic acid), and poly(caprolactone); poly(anhydrides); poly(orthoesters); poly(carbonates); and chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), copolymers and mixtures thereof.

Representative synthetic, non-degradable polymers include: poly(ethers) such as poly(ethylene oxide), poly(ethylene glycol), and poly(tetramethylene oxide); vinyl polymers - poly(acrylates) and poly(methacrylates) such as methyl, ethyl, other alkyl, hydroxyethyl methacrylate, acrylic and methacrylic acids, and others such as poly(vinyl alcohol), poly(vinyl pyrolidone), and poly(vinyl acetate); poly(urethanes); cellulose and its derivatives such as alkyl, hydroxyalkyl, ethers, esters, nitrocellulose, and various cellulose acetates; poly(siloxanes); and any chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), copolymers and mixtures thereof.

Molecules to be released

Any natural or synthetic, organic or inorganic molecule or mixture thereof can be delivered. In one embodiment, the microchip is used to deliver drugs systemically to a patient in need thereof. In another embodiment, the construction and placement of the microchip in a patient enables the localized release of drugs that may be too potent for systemic delivery. As used herein, drugs are organic or inorganic molecules, including proteins, nucleic acids, polysaccharides and synthetic organic molecules, having a bioactive effect, for example, anaesthetics, vaccines, chemotherapeutic agents, hormones, metabolites, sugars, immunomodulators, antioxidants, ion channel regulators, and antibiotics. The drugs can be in the form of a single drug or drug mixtures and can include pharmaceutically acceptable carriers. In another embodiment, molecules are released *in vitro* in any system where the controlled release of a small (milligram to nanogram) amount of one or more molecules is required, for example, in the fields of analytic chemistry or medical diagnostics. Molecules can be effective as pH buffering agents, diagnostic agents, and reagents in complex reactions such as the polymerase chain reaction or other nucleic acid amplification procedures.

Reservoir caps

In the passive timed release drug delivery devices, the reservoir caps are formed from a material that degrades or dissolves over time, or does not degrade or dissolve but is permeable to the molecules to be delivered. These materials are preferably polymeric materials. Materials can be selected for use as reservoir caps to give a variety of degradation rates or dissolution rates or permeabilities to enable the release of molecules from different reservoirs at different times and, in some cases, different rates. To obtain different release times (amounts of release time delay), caps can be formed of different polymers, the same polymer with different degrees of crosslinking, or a UV polymerizable polymer. In the latter case, varying the exposure of this polymer to UV light results in varying degrees of crosslinking and gives the cap material different

diffusion properties or degradation or dissolution rates. Another way to obtain different release times is by using one polymer, but varying the thickness of that polymer. Thicker films of some polymers result in delayed release time. Any combination of polymer, degree of crosslinking, or polymer thickness can be modified to obtain a specific release time or rate. In one embodiment, the release system containing the molecules to be delivered is covered by a degradable cap material which is nearly impermeable to the molecules. The time of release of the molecules from the reservoir will be limited by the time necessary for the cap material to degrade or dissolve. In another embodiment, the cap material is non-degradable and is permeable to the molecules to be delivered. The physical properties of the material used, its degree of crosslinking, and its thickness will determine the time necessary for the molecules to diffuse through the cap material. If diffusion out of the release system is limiting, the cap material delays the onset of release. If diffusion through the cap material is limiting, the cap material determines the release rate of the molecules in addition to delaying the onset of release.

In the active timed release devices, the reservoir caps consist of a thin film of conductive material that is deposited over the reservoir, patterned to a desired geometry, and serves as an anode. Cathodes are also fabricated on the device with their size and placement dependent on the device's application and method of electric potential control. The anode is defined as the electrode where oxidation occurs. Any conductive material capable of dissolving into solution or forming soluble ions or oxidation compounds upon application of an electric potential can be used for the fabrication of the anodes and cathodes. In addition, materials that normally form insoluble ions or oxidation products in response to an electric potential can be used if, for example, local pH changes near the anode cause these oxidation products to become soluble. Examples of suitable reservoir cap materials include metals such as copper, gold, silver, and zinc, and some polymers, as described, for example, by I.C.

Kwon *et al.*, "Electrically erodible polymer gel for controlled release of drugs", *Nature,* **1991**, 354, 291-93; and Y.H. Bae *et al.*, "Pulsatile drug release by electric stimulus", *ACS Symposium Series,* **1994**, 545, 98-110.

Device packaging, control circuitry, and power source

Microelectronic device packages are typically made of an insulating or dielectric material such as aluminum oxide or silicon nitride. Their purpose is to allow all components of the device to be placed in close proximity and to facilitate the interconnection of components to power sources and to each other. For *in vivo* applications of the delivery device, the entire package, including all components (i.e. the device, the microprocessor, and the power source), are coated or encapsulated in a biocompatible material such as poly(ethylene glycol) or polytetrafluoroethylene-like materials. The materials requirements for *in vitro* applications may be less stringent and depend on the particular situation.

The control circuitry consists of a timer, a demultiplexer, a microprocessor, and a input source, for example, a memory source, a signal receiver, or a biosensor. The timer and demultiplexer circuitry can be designed and incorporated directly onto the surface of the microchip during electrode fabrication. The criteria for selection of a microprocessor are small size, low power requirement, and the ability to translate the output from memory sources, signal receivers, or biosensors into an address for the direction of power through the demultiplexer to a specific reservoir on the delivery device. Selection of a source of input to the microprocessor such as memory sources, signal receivers, or biosensors depends on the delivery device's particular application and whether device operation is preprogrammed, controlled by remote means, or controlled by feedback from its environment (i.e. biofeedback).

The criteria for selection of a power source are small size, sufficient power capacity, ability to be integrated into the control circuitry, the ability to be recharged, and the length of time before recharging is necessary. Several lithium-based, rechargeable

microbatteries have been described by S.D. Jones and J.R. Akridge, "Development and performance of a rechargeable thin-film solid-state microbattery", *Journal of Power Sources,* **1995**, 54, 63-67; and J.B. Bates *et al.*, "New amorphous thin-film lithium electrolyte and rechargeable microbattery", *IEEE 35th International Power Sources Symposium,* **1992**, 337-39. These batteries are typically only ten microns thick and occupy 1 cm^2 of area. One or more of these batteries can be incorporated directly onto the delivery device.

METHODS OF DEVICE FABRICATION

Fabrication of the reservoirs

Devices are manufactured using methods known to those skilled in the art, reviewed, for example, by Wolf *et al.* (1986); and Jaeger (1988); Kwon *et al.* (1991).

In a preferred method of microchip manufacture, depicted in Figures 1 and 2, passive and active devices, respectively, fabrication begins by depositing and photolithographically patterning a material, typically an insulating or dielectric material, onto the substrate to serve as an etch mask during reservoir etching. Typical insulating materials for use as a mask include silicon nitride, silicon dioxide, and some polymers, such as polyimide. In a preferred embodiment, a thin film (approximately 1000-3000 Å) of amorphous silicon nitride (SiN_X) is deposited on both sides of a silicon wafer 30/300 by Plasma Enhanced Chemical Vapor Deposition (PECVD). Alternatively, a low stress, silicon-rich nitride can be deposited in a Vertical Tube Reactor (VTR), or a stoichiometric, polycrystalline nitride can be deposited by Low Pressure Chemical Vapor Deposition (LPCVD). Reservoirs are patterned into the silicon nitride film on one side of the wafer 32/320 by ultraviolet photolithography and either plasma etching or a chemical etch consisting of hot phosphoric acid. The patterned silicon nitride serves as an etch mask for the chemical etching of the exposed silicon 34/340 by a concentrated potassium hydroxide solution (approximately 38.5% wt. at a temperature of 80-85°C). Alternatively, the reservoirs can be etched into the substrate

by dry etching techniques such as reactive ion etching or ion beam etching. These techniques are commonly used in the fabrication of microelectronic devices, as reviewed, for example, by Wolf *et al.* (1986) and Jaeger (1988). Use of these microfabrication techniques allows the incorporation of hundreds to thousands of reservoirs on a single microchip. In a passive device, the reservoirs may be as little as one μm apart. In an active device, the distance between the reservoirs may be slightly larger (approximately 10-15 μm) due to the space occupied by the electrodes on or near each reservoir. Reservoirs can be made in nearly any shape and depth, and need not pass completely through the substrate. In a preferred embodiment, the reservoirs etched into a (100) silicon substrate by potassium hydroxide are in the shape of a square pyramid having side walls sloped at 54° and pass completely through the substrate (approximately 300 μm) to the silicon nitride film on the other side of the substrate, forming a SiN_4 membrane. (Here, the silicon nitride film serves as a potassium hydroxide etch stop.) The pyramidal shape allows easy filling of the reservoirs through the large opening of the reservoir (approximately 500 μm by 500 μm) on the patterned side of the substrate, release through the small opening of the reservoir (approximately 30 μm by 30 μm) on the other side of the substrate, and provides a large cavity inside the device for storing the drugs or other molecules to be delivered.

Fabrication of passive timed release reservoir caps

In the fabrication of passive timed release microchips, the reservoir cap material is injected with a micro-syringe 36a, printed with an inkjet printer cartridge, or spin coated 36b into a reservoir having the thin film of insulating mask material still present over the small opening of the reservoir. If injection or inkjet printing methods are used, cap formation is complete after the material is injected or printed into the reservoir 38a and does not require further processing. If spin coating is used, the cap material is planarized by multiple spin coatings 36b. The surface of the film is then etched by a plasma, an ion beam, or chemical etchant until the desired cap thickness is obtained 38b. In a preferred

embodiment, the insulating material used is silicon nitride and the cap material is printed into the reservoir with an inkget cartridge filled with a solution of the cap material.

Reservoir caps control the time at which molecules are released from the reservoirs. Each reservoir cap can be of a different thickness or have different physical properties to vary the time at which each release system containing the molecules is exposed to the surrounding fluids. Injection, inkjet printing, and spin coating are the preferred methods of reservoir filling and any of these methods may be used to fill reservoirs, regardless of the reservoir's shape or size. However, injection and inkjet printing are the preferred methods of filling deep (greater than 10 μm) reservoirs or reservoirs with large openings (greater than 100 μm). For example, to obtain different cap thicknesses using injection, different amounts of cap material are injected or printed directly into each individual reservoir. Spin coating is the preferred method of filling shallow (less than 10 μm) reservoirs, reservoirs that do not pass completely through the substrate, or reservoirs with small (less than 100 μm) openings. Variation in cap thickness or material by spin coating can be achieved by a repeated, step-wise process of spin coating, masking selected reservoirs, and etching. For example, to vary cap thickness with spin coating, the cap material is spin coated over the entire substrate. Spin coating is repeated, if necessary, until the material is nearly planarized. A mask material such as photoresist is patterned to cover the cap material in all the reservoirs except one. Plasma, ion beam, or chemical etchant are used to etch the cap material in the exposed reservoir to the desired thickness. The photoresist is then removed from the substrate. The process is repeated as a new layer of photoresist is deposited and patterned to cover the cap material in all the reservoirs except one (the exposed reservoir is not the same one already etched to its desired thickness). Etching of the exposed cap material in this reservoir continues until the desired cap thickness is obtained. This process of depositing and patterning a mask material such as photoresist, etching,

and mask removal can be repeated until each reservoir has its own unique cap thickness. The techniques, UV photolithography, plasma or ion beam etching, etc., are well known to those skilled in the field of microfabrication.

Although injection, inkjet printing and spin coating are the preferred methods of cap fabrication, it is understood that each reservoir can be capped individually by capillary action, by pulling or pushing the material into the reservoir using a vacuum or other pressure gradient, by melting the material into the reservoir, by centrifugation and related processes, by manually packing solids into the reservoir, or by any combination of these or similar reservoir filling techniques.

Once a cap fabrication method is selected, additional methods for controlling the time of release of molecules from a reservoir can be utilized. Two non-limiting examples include either UV polymerizable polymers or the layering of release system and cap materials. First, if the reservoir caps are made of either an injected, inkjet printed or spin coated UV polymerizable polymer, each cap can be exposed to a different intensity of UV light to give varying degrees of crosslinking and therefore, different degradation or dissolution rates for degradable caps or different permeabilities to the molecules for non-degradable caps. Second, layers of cap material, both degradable and non-degradable, can be inserted between layers of the release system containing the molecules to be delivered by injection, inkjet printing, spin coating, or selective crosslinking. These and other similar methods allow complex release profiles (i.e. pulsatile delivery at irregular time intervals) to be achieved from a single reservoir.

If desired, a passive timed release device can be fabricated without reservoir caps. The rate of release of the molecules is thus solely controlled by the physical and material properties of the release system containing the molecule to be delivered.

Fabrication of active timed release reservoir caps

In a preferred embodiment, photoresist is patterned in the form of electrodes on the surface of the substrate having the reservoirs covered by the thin membrane of insulating or dielectric material. The photoresist is developed such that the area directly over the covered opening of the reservoir is left uncovered by photoresist and is in the shape of an anode. A thin film of conductive material capable of dissolving into solution or forming soluble ions or oxidation compounds upon the application of an electric potential is deposited over the entire surface using deposition techniques such as chemical vapor deposition, electron or ion beam evaporation, sputtering, spin coating, and other techniques known in the art. Exemplary materials include metals such as copper, gold, silver, and zinc and some polymers, as disclosed by Kwon *et al.* (1991) and Bae *et al.* (1994). After film deposition, the photoresist is stripped from the substrate. This removes the deposited film, except in those areas not covered by photoresist (lift-off technique). This leaves conducting material on the surface of the substrate in the form of electrodes 360. An alternative method involves depositing the conductive material over the entire surface of the device, patterning photoresist on top of the conductive film using UV or infrared (IR) photolithography, so that the photoresist lies over the reservoirs in the shape of anodes, and etching the unmasked conductive material using plasma, ion beam, or chemical etching techniques. The photoresist is then stripped, leaving conductive film anodes covering the reservoirs. Typical film thicknesses of the conductive material may range from 0.05 to several microns. The anode serves as the reservoir cap and the placement of the cathodes on the device is dependent upon the device's application and method of electric potential control.

An insulating or dielectric material such as silicon oxide (SiO_x) or silicon nitride (SiN_x) is deposited over the entire surface of the device by methods such as chemical vapor deposition (CVD), electron or ion beam evaporation, sputtering, or spin coating. Photoresist is patterned on top

of the dielectric to protect it from etching except on the cathodes and the portions of the anodes directly over each reservoir 380. The dielectric material can be etched by plasma, ion beam, or chemical etching techniques. The purpose of this film is to protect the electrodes from corrosion, degradation, or dissolution in all areas where electrode film is not necessary for release.

The electrodes are positioned in such a way that when an electric between an anode and a cathode, the unprotected (not covered by dielectric) portion of the anode reservoir cap oxidizes to form soluble compounds or ions that dissolves into solution, exposing the release system containing the molecules to the surrounding fluids. The molecules are released from the reservoir at a rate dependent upon the degradation or dissolution rate of a degradable release system or the rate of diffusion of the molecules out of or through a non-degradable release system.

Removal of the insulator membrane (reservoir etch stop)

The thin membrane of insulating or dielectric material covering the reservoir used as a mask and an etch stop during reservoir fabrication must be removed from the active timed release device before filling reservoir 400 and from the passive timed release device (if the reservoir extends completely through the substrate) after filling reservoir 44. The film may be removed in two ways. First, the film can be removed by an ion beam or reactive ion plasma. In a preferred embodiment, the silicon nitride film used as the insulating material can be removed by a reactive ion plasma composed of oxygen and fluorine containing gases such as CHF_3 or CF_4. Second, the film can be removed by chemical etching. For example, buffered hydrofluoric acid (BHF or BOE) can be used to etch silicon dioxide and hot phosphoric acid can be used to etch silicon nitride.

Reservoir filling

The release system containing the molecules for delivery is inserted into the large opening of the reservoir by injection, inkjet printing or spin coating 40a/40b/400. Each reservoir can contain a different molecule and dosage. Similarly, the release kinetics of the molecule in each reservoir can be varied by the choice of the release system and cap materials. In addition, the mixing or layering of release system and cap materials in each reservoir can be used to tailor the release kinetics to the needs of a particular application.

The distribution over the microchip of reservoirs filled with the release system containing the molecules to be delivered can vary depending on the medical needs of the patient or other requirements of the system. For applications in drug delivery, for example, the drugs in each of the rows can differ from each other. One row may contain a hormone and another row may contain a metabolite. Also, the release system can differ within each row to release a drug at a high rate from one reservoir and a slow rate from another reservoir. The dosages can also vary within each row. For those devices having deep (greater than 10 μm) reservoirs or reservoirs with large (greater than 100 μm) openings, differences in reservoir loading can be achieved by injection or inkjet printing of different amounts of material directly into each reservoir. Variation between reservoirs is achieved in devices having shallow (less than 10 μm) reservoirs, reservoirs that do not pass completely through the substrate, or reservoirs with small (less than 100 μm) openings by a repeated, step-wise process of masking selected reservoirs, spin coating, and etching, as described above regarding the fabrication by spin coating of passive timed release reservoir caps. Preferably, the release system and molecules to be delivered are mixed before application to the reservoirs. Although injection, inkjet printing and spin coating are the preferred methods of filling reservoirs, it is understood that each reservoir can be filled individually by capillary action, by pulling or pushing the material into the reservoir using a vacuum or other pressure gradient, by

melting the material into the reservoir, by centrifugation and related processes, by manually packing solids into the reservoir, or by any combination of these or similar reservoir filling techniques.

Device packaging, control circuitry, and power source

The openings through which the reservoirs of passive and active devices are filled are sealed by wafer bonding or with a waterproof epoxy or other appropriate material impervious to the surrounding fluids 44/440. For *in vitro* applications, the entire unit, except for the face of the device containing the reservoirs and electrodes, is encased in a material appropriate for the system. For *in vivo* applications, the unit would be encapsulated in a biocompatible material such as poly(ethylene glycol) or polytetrafluoroethylene.

The mechanism for release of molecules by the active timed release device does not depend on multiple parts fitted or glued together which must retract or dislodge. Control of the time of release of each reservoir can be achieved by a preprogrammed microprocessor, by remote control, by a signal from a biosensor, or by any combination of these methods, as shown schematically in Figure 3. First, a microprocessor is used in conjunction with a source of memory such as programmable read only memory (PROM), a timer, a demultiplexer, and a power source such as a microbattery, such as is described, for example, by Jones *et al.* (1995) and Bates *et al.* (1992). The release pattern is written directly into the PROM by the user. The PROM sends these instructions to the microprocessor. When the time for release has been reached as indicated by the timer, the microprocessor sends a signal corresponding to the address (location) of a particular reservoir to the demultiplexer. The demultiplexer sends an input, such as an electric potential, to the reservoir addressed by the microprocessor. A microbattery provides the power to operate the PROM, timer, and microprocessor, and provides the electric potential input that is directed to a particular reservoir by the demultiplexer. The manufacture, size, and location of each of these components is dependent upon the requirements of a particular

application. In a preferred embodiment, the memory, timer, microprocessor, and demultiplexer circuitry is integrated directly onto the surface of the chip. The microbattery is attached to the other side of the chip and is connected to the device circuitry by vias or thin wires. However, in some cases, it is possible to use separate, prefabricated, component chips for memory, timing, processing, and demultiplexing. These are attached to the backside of the miniaturized delivery device with the battery. The size and type of prefabricated chips used depends on the overall dimensions of the delivery device and the number of reservoirs. Second, activation of a particular reservoir by the application of an electric potential can be controlled externally by remote control. Much of the circuitry used for remote control is the same as that used in the preprogrammed method. The main difference is that the PROM is replaced by a signal receiver. A signal such as radio waves, low power laser, or ultrasound is sent to the receiver by an external source, for example, computers or ultrasound generators. The signal is sent to the microprocessor where it is translated into a reservoir address. Power is then directed through the demultiplexer to the reservoir having the appropriate address. Third, a biosensor is integrated into the microchip to detect molecules in the surrounding fluids. When the concentration of the molecules reaches a certain level, the sensor sends a signal to the microprocessor to activate one or more reservoirs. The microprocessor directs power through the demultiplexer to the particular reservoir(s).

Electric Potential Control Methods

The reservoir caps of an active device are anodes that oxidize to form soluble compounds and ions when a potential is applied between the anode and a cathode. For a given electrode material and electrolyte, there exists a range of electric potentials over which these oxidation reactions are thermodynamically and kinetically favorable. In order to reproducibly oxidize and open the device's reservoir caps, the anode potential must be maintained in this potential range.

There exist two primary control methods for maintaining an electrode within a specific potential range. The first method is called potentiostatic control. As the name indicates, the potential is kept constant during reservoir activation. Control of the potential is typically accomplished by incorporating a third electrode into the system that has a known, constant potential, called a reference electrode. The reference electrode can take the form of an external probe whose tip is placed within one to three mm of the anode surface. The potential of the anode is measured and controlled with respect to the known potential of a reference electrode such as a saturated calomel electrode (SCE). In a preferred embodiment of potentiostatic control, a thin film reference electrode and potential feedback controller circuitry could be fabricated directly onto the surface of the microchip. For example, a microfabricated Ag/AgCl reference electrode integrated with a microchip device would enable the device to maintain the anode potential of an activated reservoic within the oxidation regime until the reservoir was completely opened. The second method is called galvanostatic control. As the name indicates, the current is kept constant during reservoir activation. One drawback to this method of control is that there is more than one stable potential for a given current density. However, if the current density versus potential behavior is well characterized for the microchip device in a particular electrolyte system, the current density that will maintain the anode in teh oxidation regime will be known. In this case, the galvanostatic method of potential control would be preferable to the potentiostatic control, because galvanostatic control does not require a reference electrode.

MICROCHIP APPLICATIONS

Passive and active microchip devices have numerous *in vitro* and *in vivo* applications. The microchip can be used *in vitro* to deliver small, controlled amounts of chemical reagents or other molecules to solutions or reaction mixtures at precisely controlled times and rates. Analytical chemistry and medical diagnostics are examples of fields where the

microchip delivery device can be used. The microchip can be used *in vivo* as a drug delivery device. The microchips can be implanted into a patient, either by surgical techniques or by injection, or can be swallowed. The microchips provide delivery of drugs to animals or persons who are unable to remember or be ambulatory enough to take medication. The microchips further provide delivery of many different drugs at varying rates and at varying times of delivery.

The present invention will be further understood by reference to the following non-limiting examples.

Example 1: Microchip with passive timed drug release.

A passive timed release device, microchip 10 is shown in Figure 4. Microchip 10 is formed from substrate 14. Reservoirs 16 are etched into substrate 14. Positioned in reservoirs 16 is a release system containing molecules 18 for delivery. The reservoirs are capped with reservoir caps 12. The release system and the molecules for delivery 18 can vary between rows 20a, 20b, 20c, and within reservoirs of each row.

Microchip 10 can be inserted into solution for *in vitro* applications or be implanted in a selected part of the body or swallowed for *in vivo* applications and left to operate without requiring further attention. When exposed to the surrounding fluids, reservoir caps 12 will degrade, dissolve or become permeable to the release system containing molecules for delivery 18.

Figures 7a-i depict several additional possible configurations for passive delivery devices.

Example 2: Microchip with active controlled time release.

A drug delivery device that provides active timed release is shown as microchip 100 in Figure 5. Microchip 100 is similar to microchip 10 except that microchip 100 contains electrodes that provide for active timed release. Microchip 100 is formed from substrate 160, release system containing molecules 180 for delivery, anode reservoir caps 120, and cathodes 140. Preferably, microchip 100 further includes an input source, a microprocessor, a timer, a demultiplexer, and a power source

(not shown). The power source provides energy to drive the reaction between selected anodes and cathodes. Upon application of a small potential between an anode and cathode, electrons pass from the anode to the cathode through the external circuit causing the anode material to oxidize and form soluble compounds or ions that dissolve into the surrounding fluids, exposing the release system containing the molecules for delivery 180 to the surrounding fluids. The microprocessor directs power to specific electrode pairs through a demultiplexer as directed by a PROM, remote control, or biosensor.

Figure 6 is a schematic of a second embodiment of a microchip 200 from from substrate 260 actively releasing drug 280 from the device upon application of an electric potential between an anode and cathode, which, unlike the device in Figure 5, includes an insulator overlayer.

Figures 8a-c depicts three additional possible configurations for active delivery devices.

We claim:

1. A microchip device for the release of molecules comprising a substrate, and

a plurality of reservoirs in the substrate, wherein the reservoirs controllably release molecules incorporated therein.

2. The device of claim 1 wherein the reservoirs comprise different types of molecules, different amounts of molecules, or combinations thereof.

3. The device of claim 1 wherein release of the molecules is controlled by a release system incorporating the molecules in the reservoir.

4. The device of claim 3 further comprising degradable reservoir caps positioned on the reservoirs over the release system, wherein the degradation rate of the cap determines the time at which the molecules are released from the reservoir.

5. The device of claim 4 wherein the reservoir caps have different thicknesses.

6. The device of claim 4 wherein the release system in a reservoir degrades or dissolves to release the molecules after the reservoir cap is degraded or dissolved.

7. The device of claim 4 wherein pulsatile release is obtained from a single reservoir by layering different release system and reservoir cap materials in the reservoir.

8. The device of claim 4 wherein the release system is non-degradable, and diffusion of the molecules out of the release system provides a pulsed release of the molecules after the degradation of the reservoir cap.

9. The device of claim 3 comprising non-degradable reservoir caps positioned on the reservoirs over the release system, wherein the rate of diffusion of the molecules through the cap determines the time at which the molecules are released from the reservoirs.

10. The device of claim 4 further comprising cathodes, a microprocessor, a timer, a demultiplexer, and a power source, wherein the reservoir caps are anodes and are each surrounded by one of the cathodes, wherein upon application of an electric potential between each cathode and anode, the reservoir cap oxidizes, dissolves in solution, and exposes the underlying release system to the surrounding fluids.

11. The device of claim 10 wherein the microprocessor function is directed by a source of memory preprogrammed to activate the electrodes of individual reservoirs at specific times.

12. The device of claim 10 wherein the microprocessor function is directed by remote control to activate the electrodes of each reservoir.

13. The device of claim 10 further comprising a biosensor, wherein the microprocessor function is directed by the biosensor to activate the electrodes of each reservoir.

14. The device of claim 2 wherein the release system comprises drug molecules in an excipient or diluent.

15. The device of claim 14 wherein the release system in each reservoir is formed of the molecules to be released, wherein the dissolution rate of the molecules determines the rate of release of the molecules.

16. A method of fabricating a device for the release of molecules comprising:

providing a substrate;

depositing and patterning an insulating material on the substrate for use as an etch mask;

etching a plurality of reservoirs in the substrate;

filling the reservoirs with release system and cap materials; and

etching release system and cap materials.

17. The method of claim 16 further comprising removing a thin film of insulating material over the reservoirs.

18. The method of claim 16 further comprising filling each reservoir with different types and amounts of cap materials and release systems containing molecules to be delivered.

19. The method of claim 16 wherein the reservoirs are filled by injection, inkjet printing or spin coating.

20. The method of claim 19 wherein the reservoirs are filled by inkjet printing.

21. The method of claim 17 further comprising depositing a thin film of conductive material over the thin film of insulating material over each reservoir.

22. The method of claim 21 further comprising patterning the conductive film into electrodes so that an anode covers each reservoir opening and a cathode surrounds each anode.

23. The method of claim 22 further comprising depositing a material over each electrode, except the anode directly over the reservoir and the cathode surrounding the exposed portion of the anode.

24. A method for the delivery of molecules comprising

providing at a site where the molecules are to be delivered a microchip device for the release of molecules comprising a substrate, and a plurality of reservoirs in the substrate, wherein the reservoirs controllably release molecules incorporated therein.

25. The method of claim 24 wherein the molecules are drugs, comprising administering, implanting or injecting the microchip into a patient.

26. The method of claim 25 wherein the molecules are a drug selected from the group consisting of nucleic acids, proteins, amino acids, polysaccharides, and organic or synthetic molecules.

27. The method of claim 26 wherein the drugs are in combination with a pharmaceutically acceptable carrier.

28. The method of claim 24 wherein the molecules are diagnostic or chemical reagents.

29. The method of claim 24 wherein the molecules are released in a pulsatile or continuous manner.

30. The method of claim 24 wherein the release system is formed by the molecules to be released.

31. The method of claim 24 wherein degradable reservoir caps are positioned on the reservoirs over the release system, wherein the degradation, dissolution or diffusion rate of the cap determines the time at which the molecules are released from the reservoir.

32. The method of claim 24 wherein the device further comprises cathodes, a microprocessor, a timer, a demultiplexer, and a power source, wherein the reservoir caps are anodes and are each surrounded by one of the cathodes, wherein the method further comprises applying an electric potential between each cathode and anode, to oxidize the reservoir cap and expose the underlying release system to the surrounding fluids.

33. The method of claim 32 wherein the microprocessor function is directed by a source of memory preprogrammed to activate the electrodes of individual reservoirs at specific times, wherein the method further comprises programming the memory.

34. The method of claim 32 wherein the microprocessor function is directed by remote control to activate the electrodes of each reservoir.

35. The method of claim 32 wherein the device further comprises a biosensor, wherein the microprocessor function is directed by the biosensor to activate the electrodes of each reservoir.

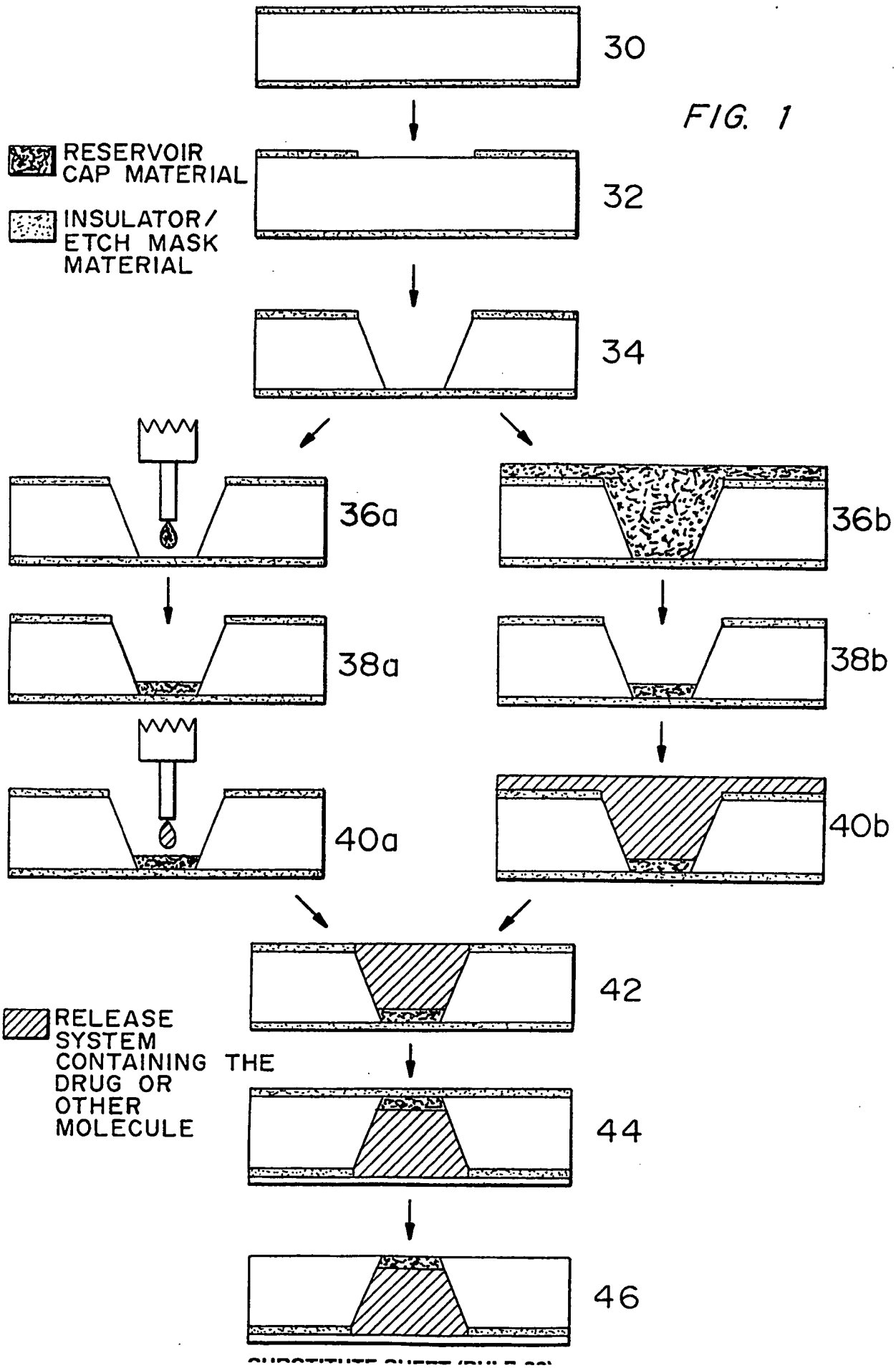

30
32
34
36a
36b
38a
38b
40a
40b
42
44
46
RESERVOIR CAP MATERIAL
INSULATOR/ ETCH MASK MATERIAL
RELEASE SYSTEM CONTAINING THE DRUG OR OTHER MOLECULE

FIG. 1

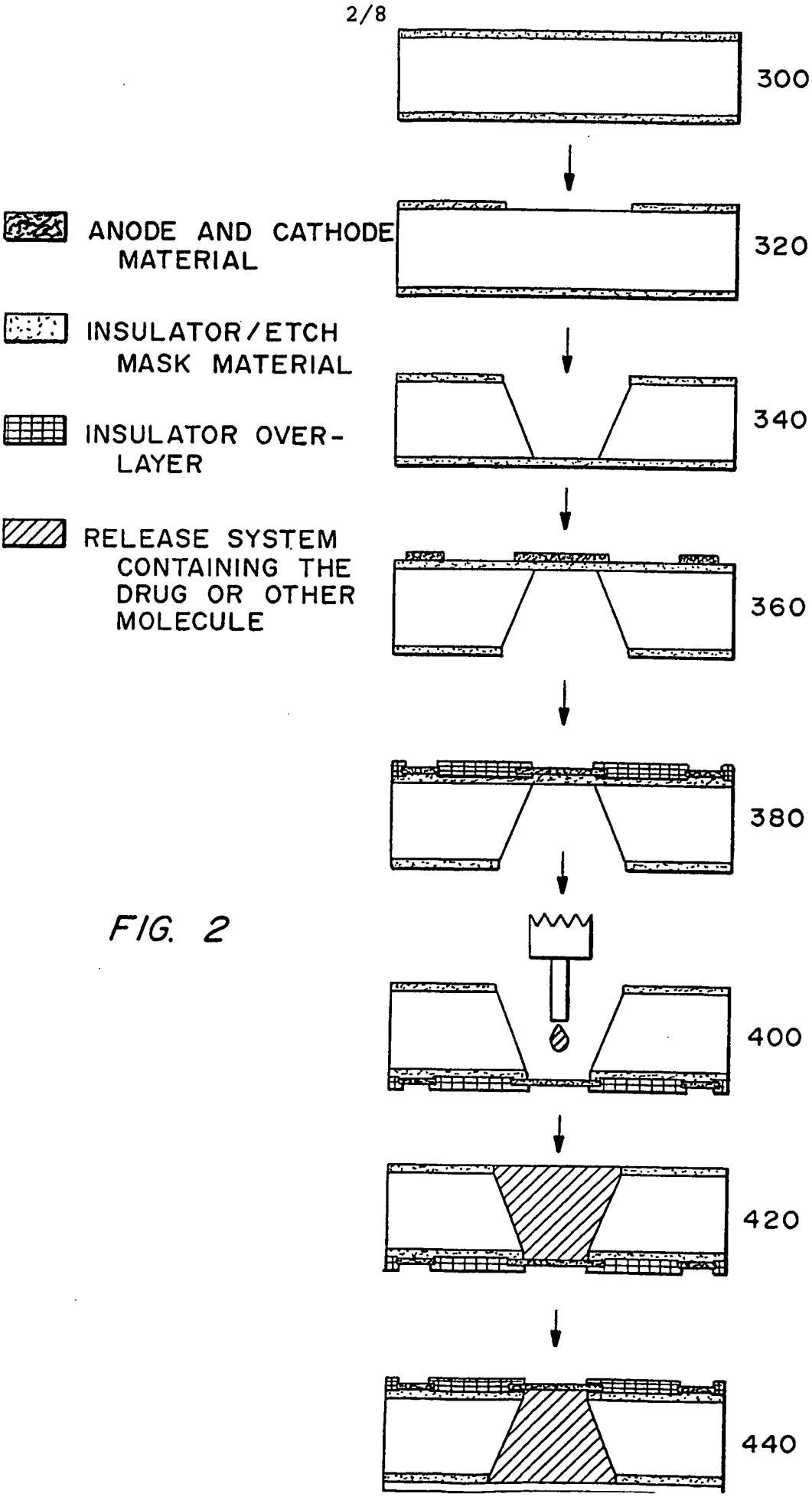

ANODE AND CATHODE MATERIAL
INSULATOR/ETCH MASK MATERIAL
INSULATOR OVER-LAYER
RELEASE SYSTEM CONTAINING THE DRUG OR OTHER MOLECULE
300
320
340
360
380
400
420
440

FIG. 2

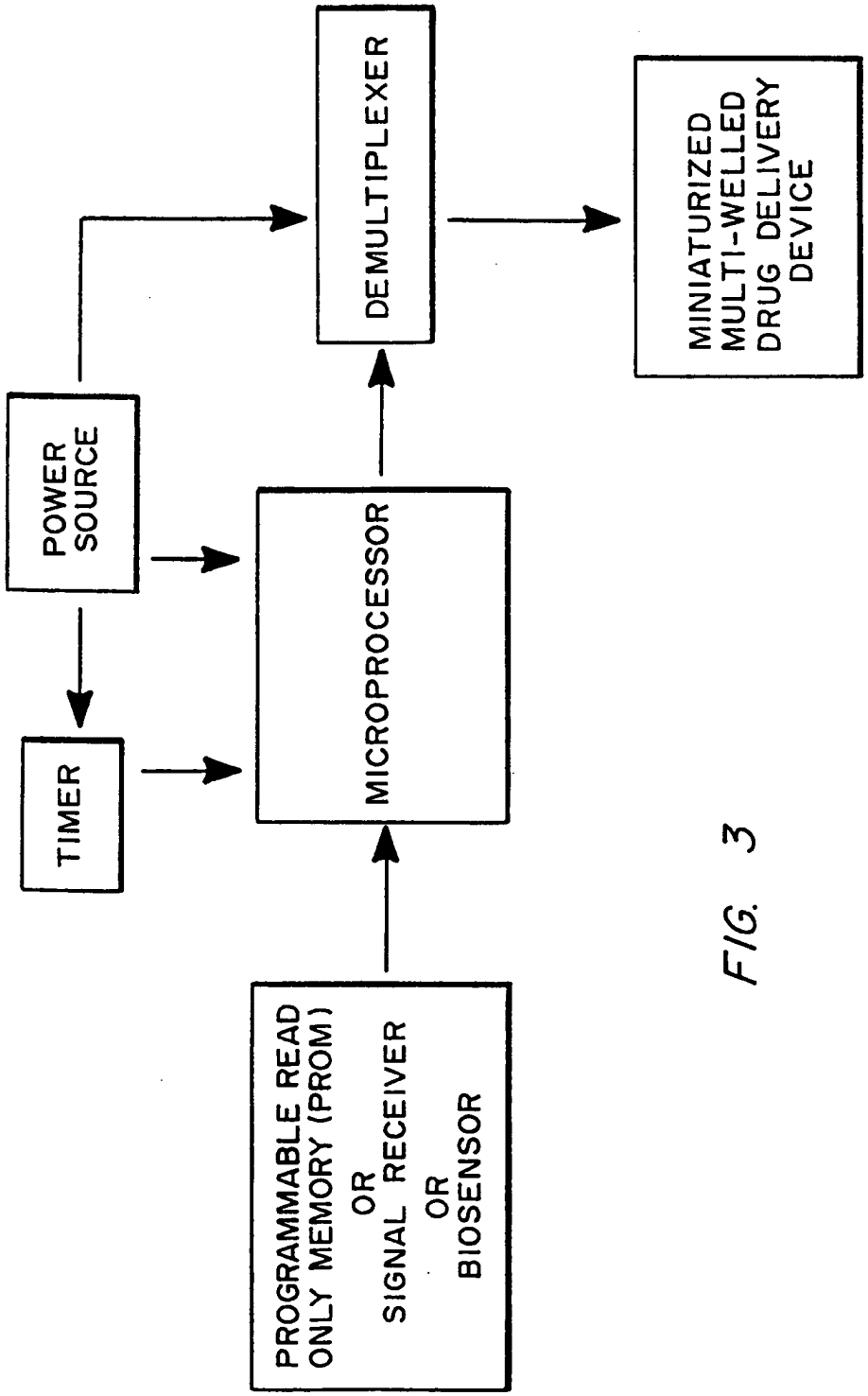
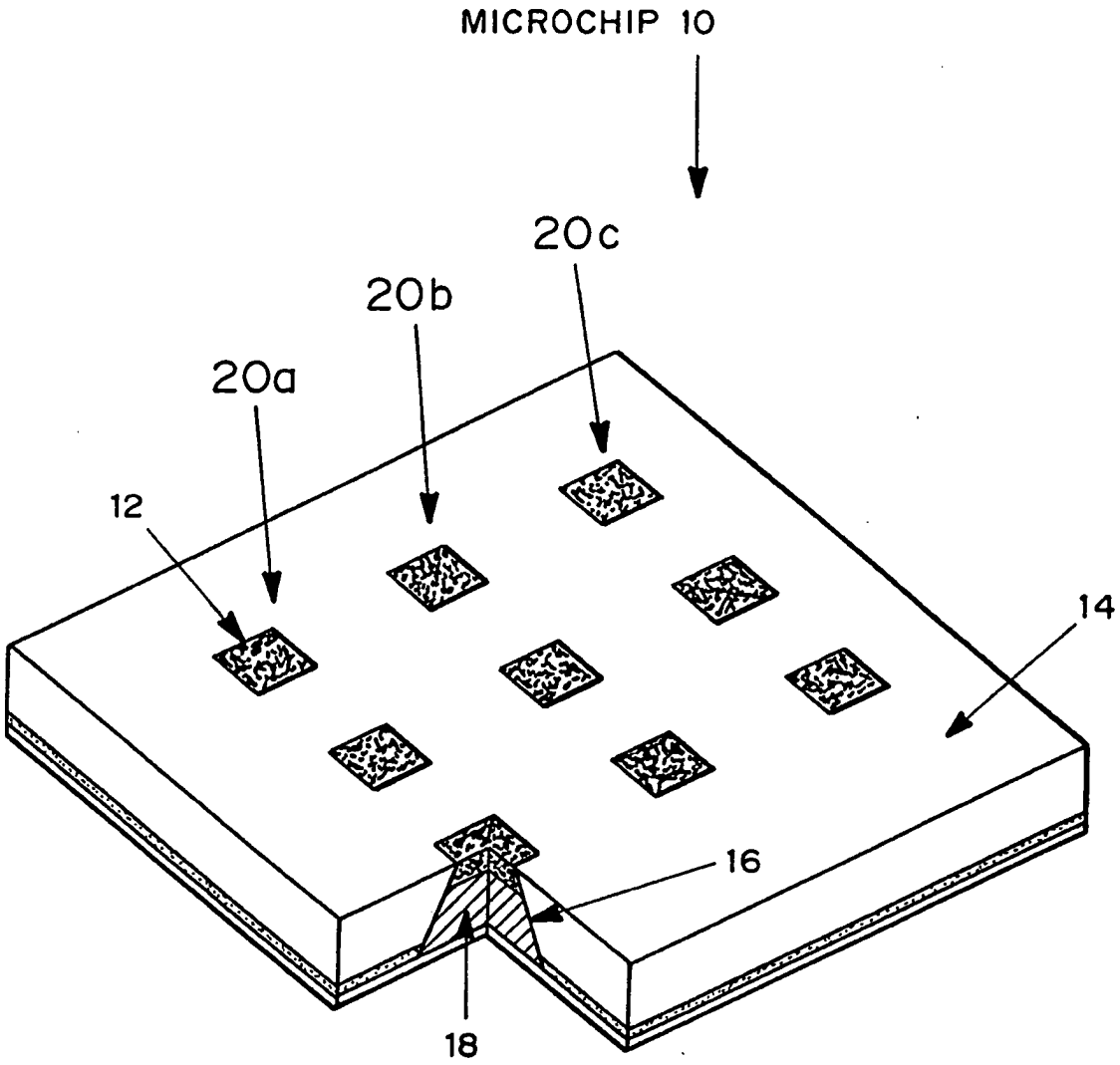

PROGRAMMABLE READ ONLY MEMORY (PROM) OR SIGNAL RECEIVER OR BIOSENSOR
TIMER
POWER SOURCE
MICROPROCESSOR
DEMULTIPLEXER
MINIATURIZED MULTI-WELLED DRUG DELIVERY DEVICE

FIG. 3



RELEASE SYSTEM CONTAINING THE DRUG OR OTHER MOLECULE

RESERVOIR CAP MATERIAL

INSULATOR/ETCH MASK MATERIAL

FIG. 4

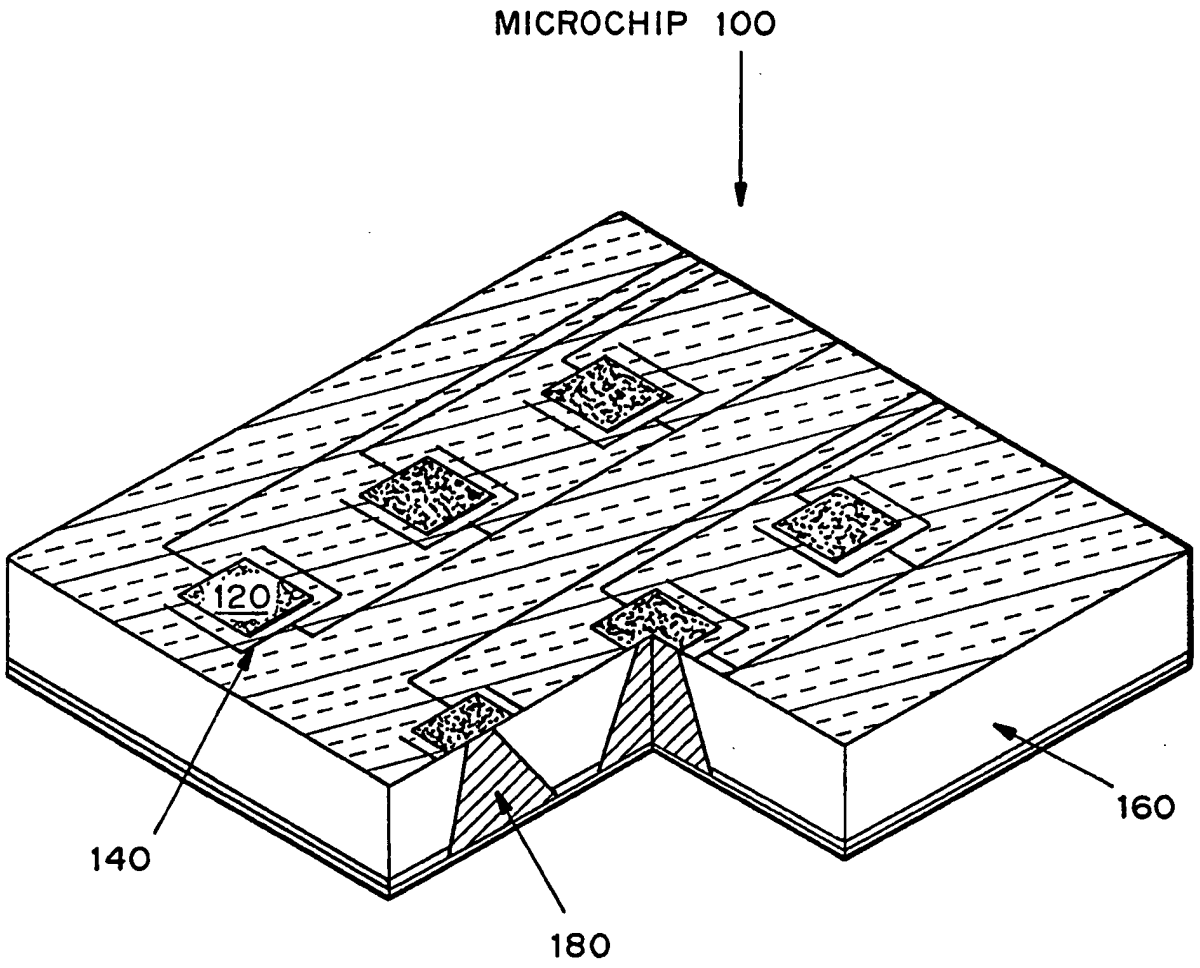
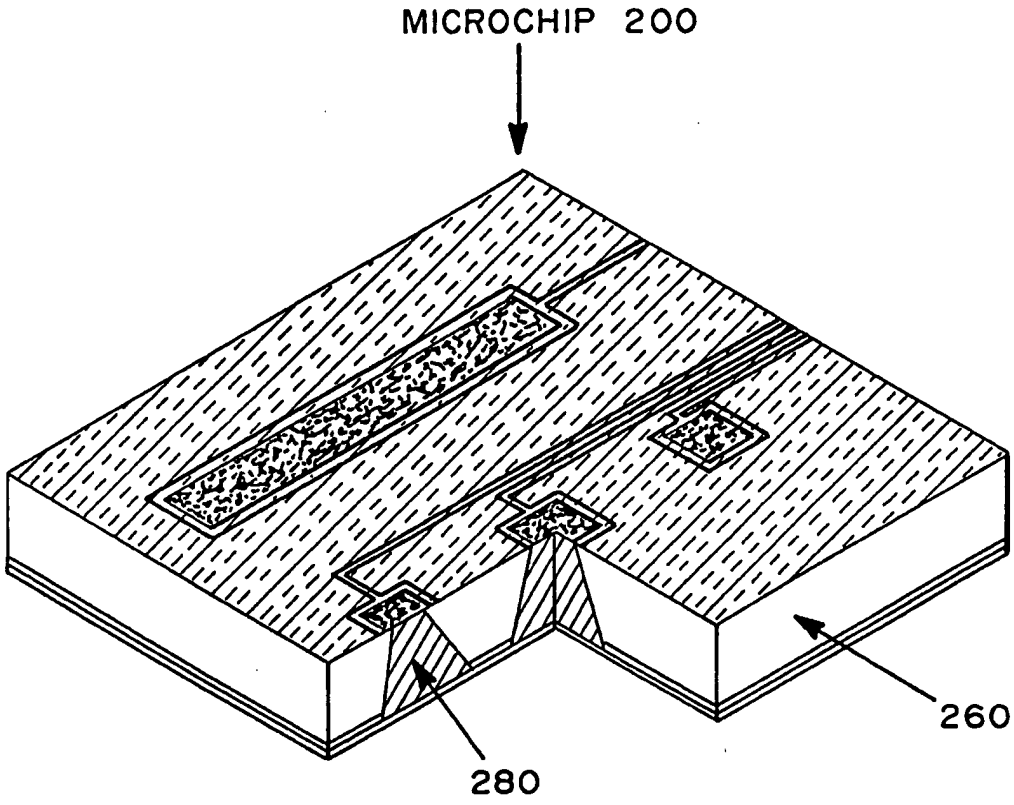

MICROCHIP 100
120
140
160
180
RELEASE SYSTEM CONTAINING THE DRUG OR OTHER MOLECULE
ANODE AND CATHODE MATERIAL
INSULATOR/ETCH MASK MATERIAL

FIG. 5



RELEASE SYSTEM CONTAINING THE DRUG OR OTHER MOLECULE

ANODE AND CATHODE MATERIAL

INSULATOR OVERLAYER AND ETCH MASK MATERIAL

FIG. 6

FIG. 7a

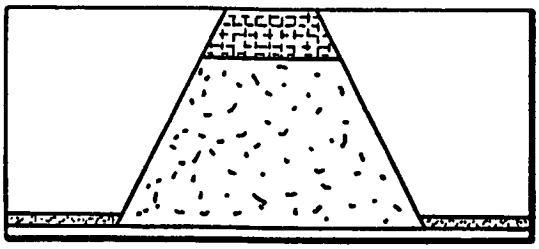


FIG. 7b

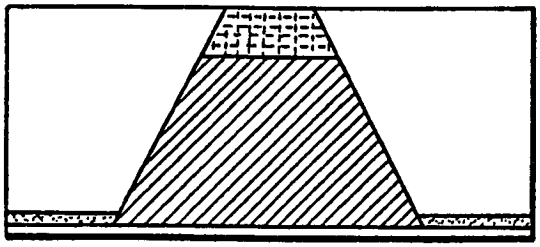


FIG. 7c

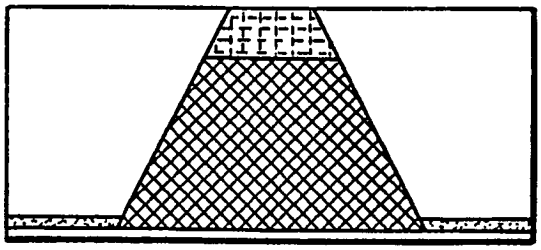


FIG. 7d

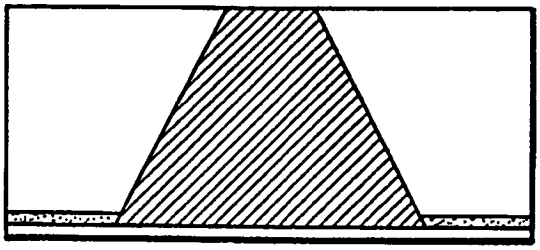


FIG. 7e

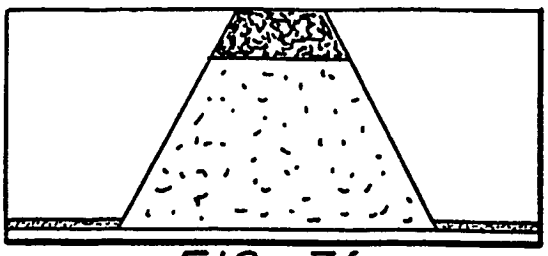


FIG. 7f

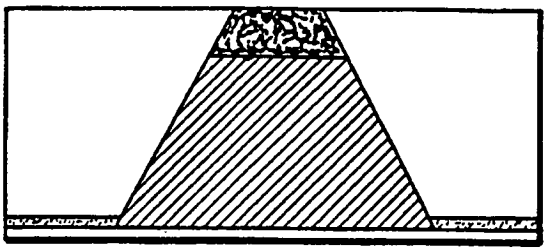


FIG. 7g

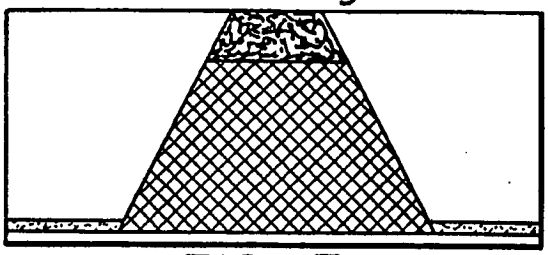


FIG. 7h

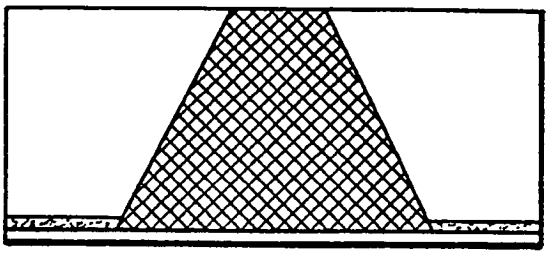
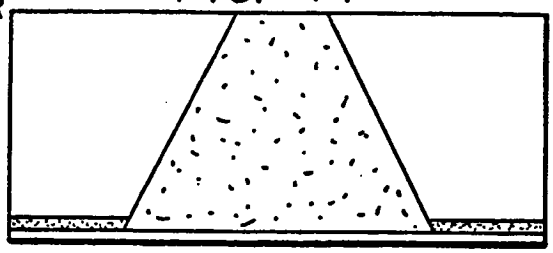
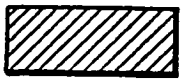


FIG. 7i

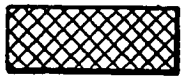


DEGRADABLE RESERVOIR CAP MATERIAL

NON-DEGRADABLE RESERVOIR-CAP MATERIAL



DEGRADABLE RELEASE SYSTEM



NON-DEGRADABLE RELEASE SYSTEM

PURE DRUG OR OTHER MOLECULE (SOLID, LIQUID, OR GEL FORM)

INSULATOR / ETCH MASK MATERIAL

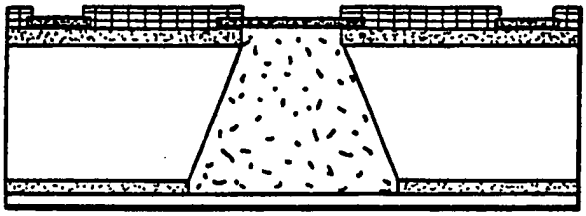


FIG. 8a

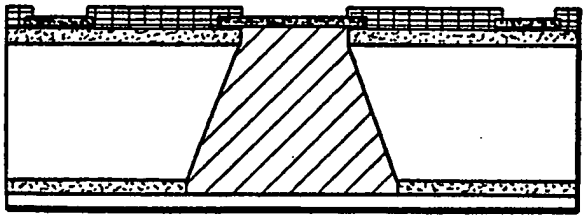


FIG. 8b

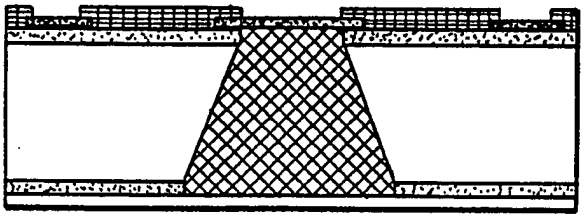


FIG. 8c

INSULATOR / ETCH MASK MATERIAL

ANODE AND CATHODE MATERIAL

INSULATOR OVERLAYER

DEGRADABLE RELEASE SYSTEM

NON-DEGRADABLE RELEASE SYSTEM

PURE DRUG OR OTHER MOLECULE (SOLID, LIQUID, OR GEL FORM)

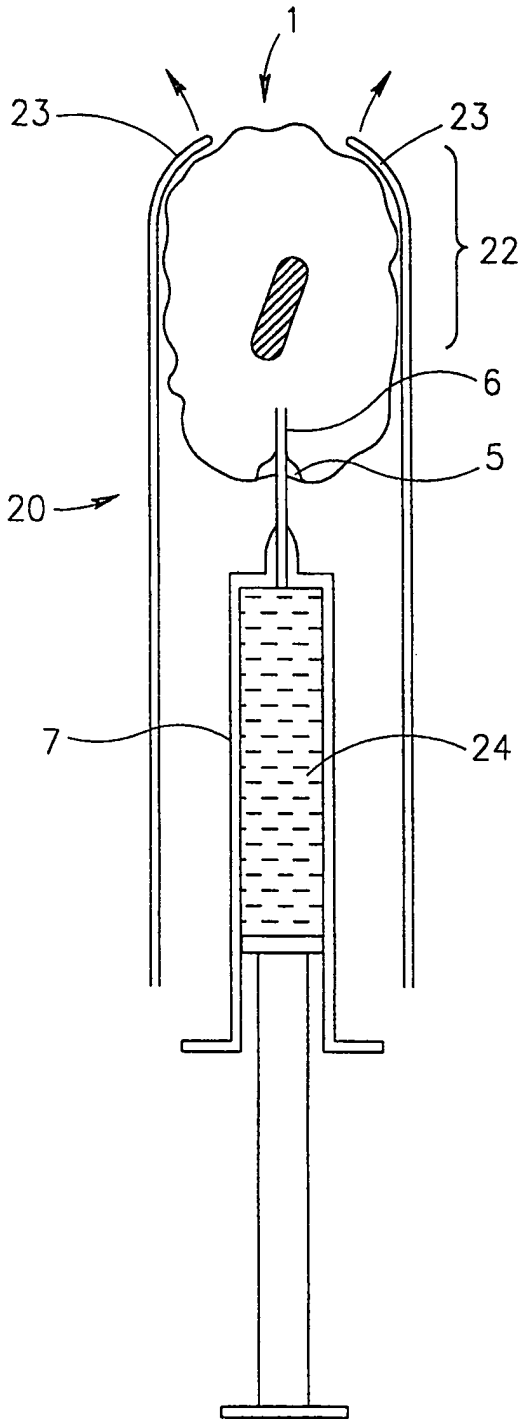


FIG.4A

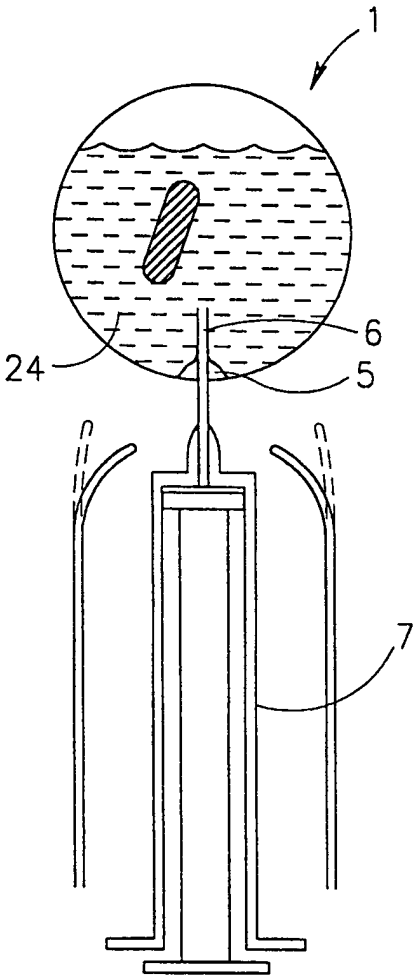


FIG.4B

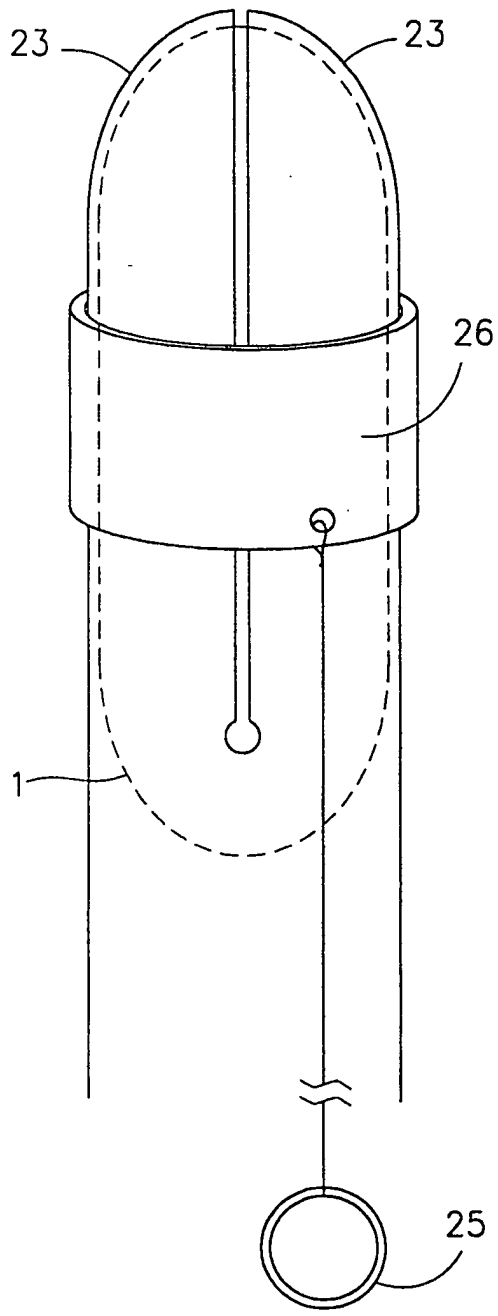


FIG.5A

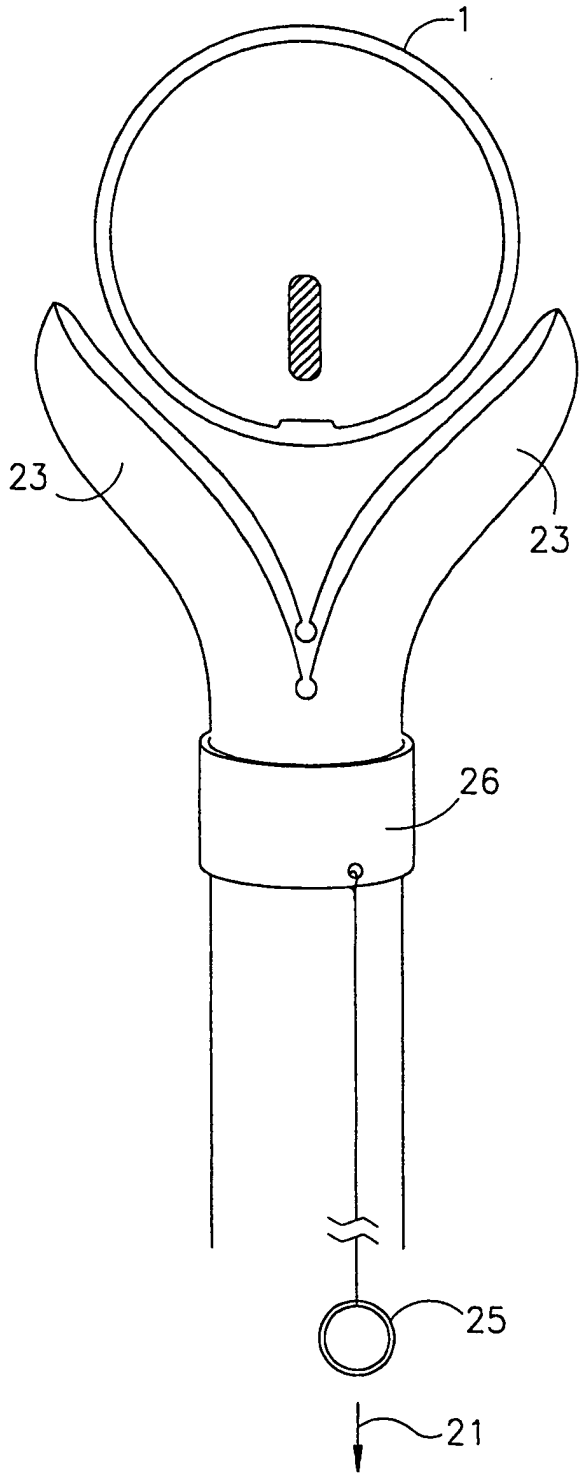
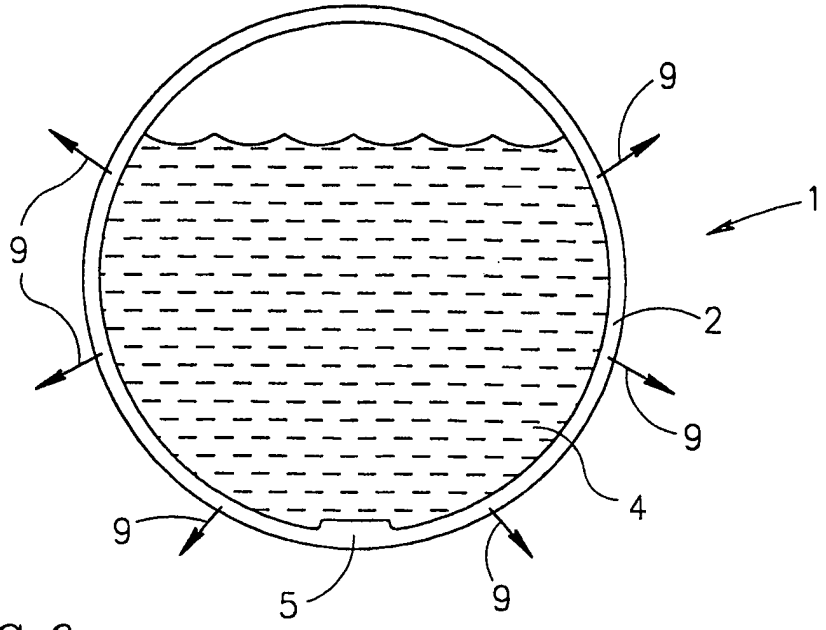


FIG.5B


9
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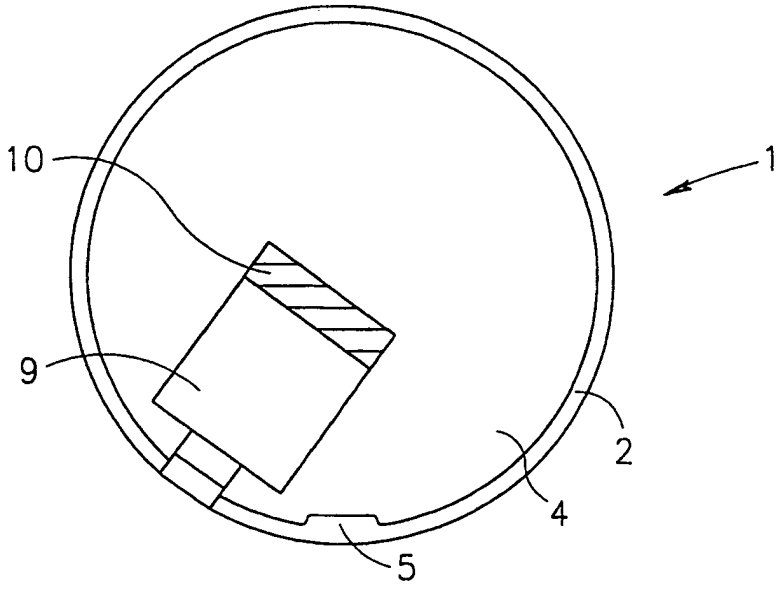
9

FIG.6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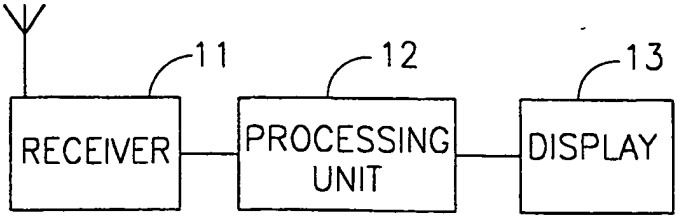
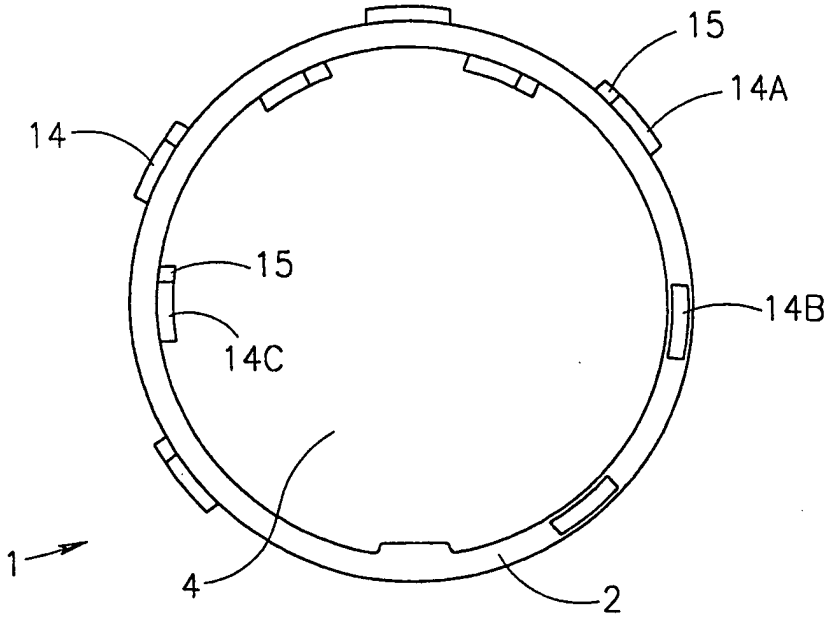
4
5

FIG.7


11
12
13
RECEIVER
PROCESSING UNIT
DISPLAY


15
14A
14
15
14B
14C
1
4
2

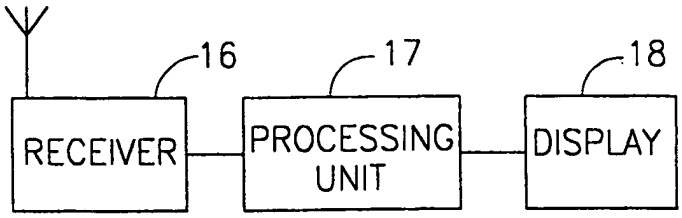

16
17
18
RECEIVER
PROCESSING UNIT
DISPLAY

FIG.8

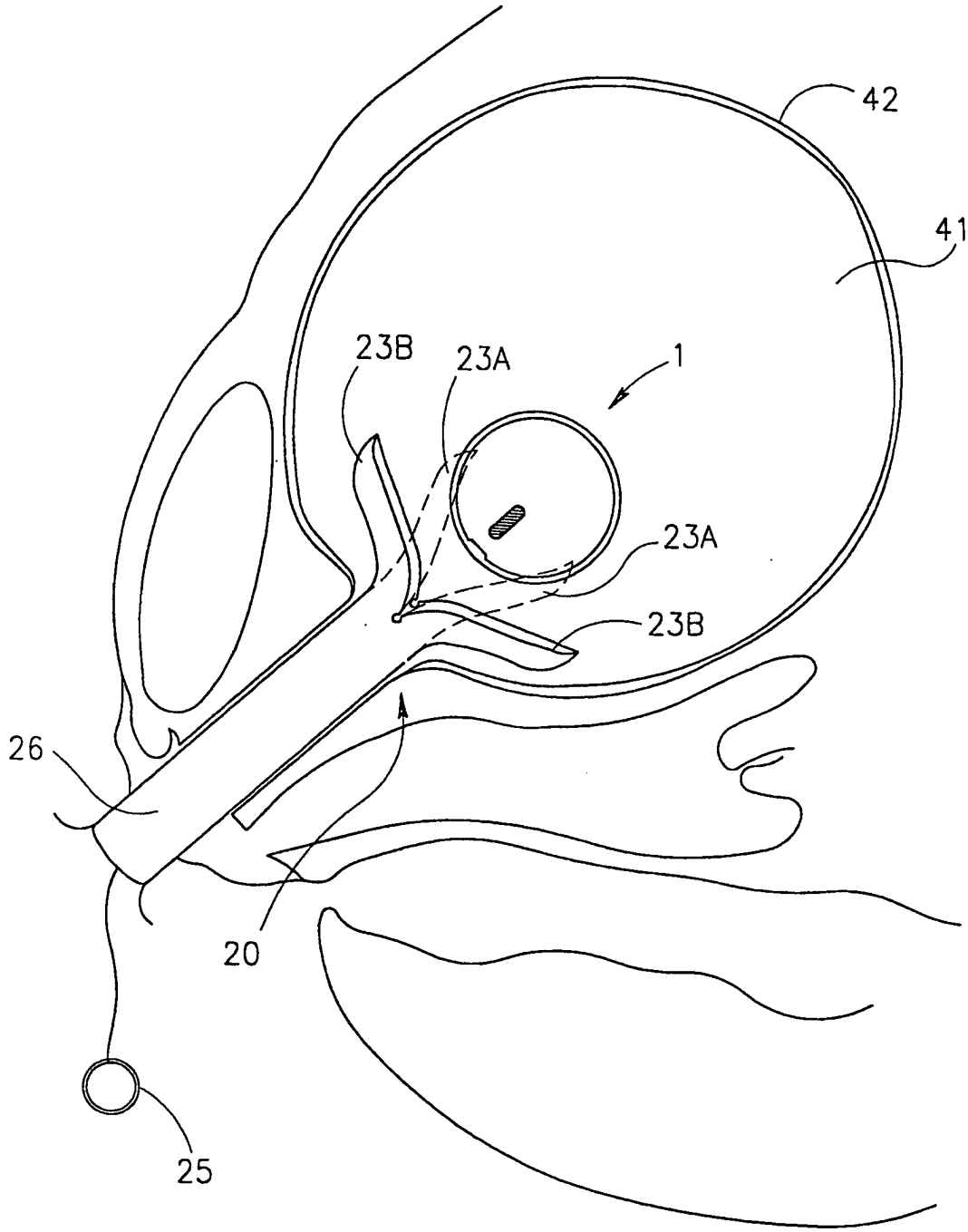


FIG.9

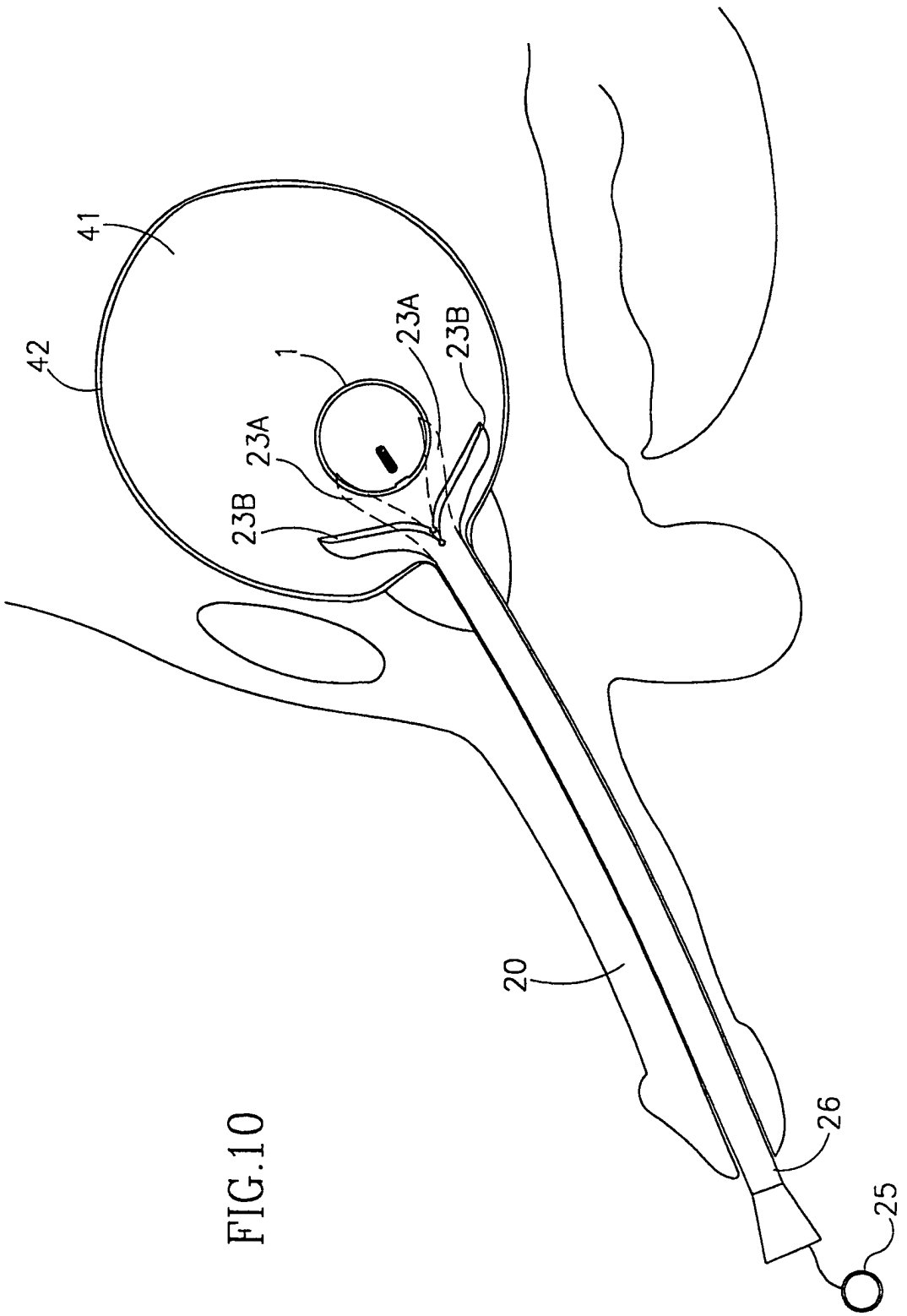


FIG.10

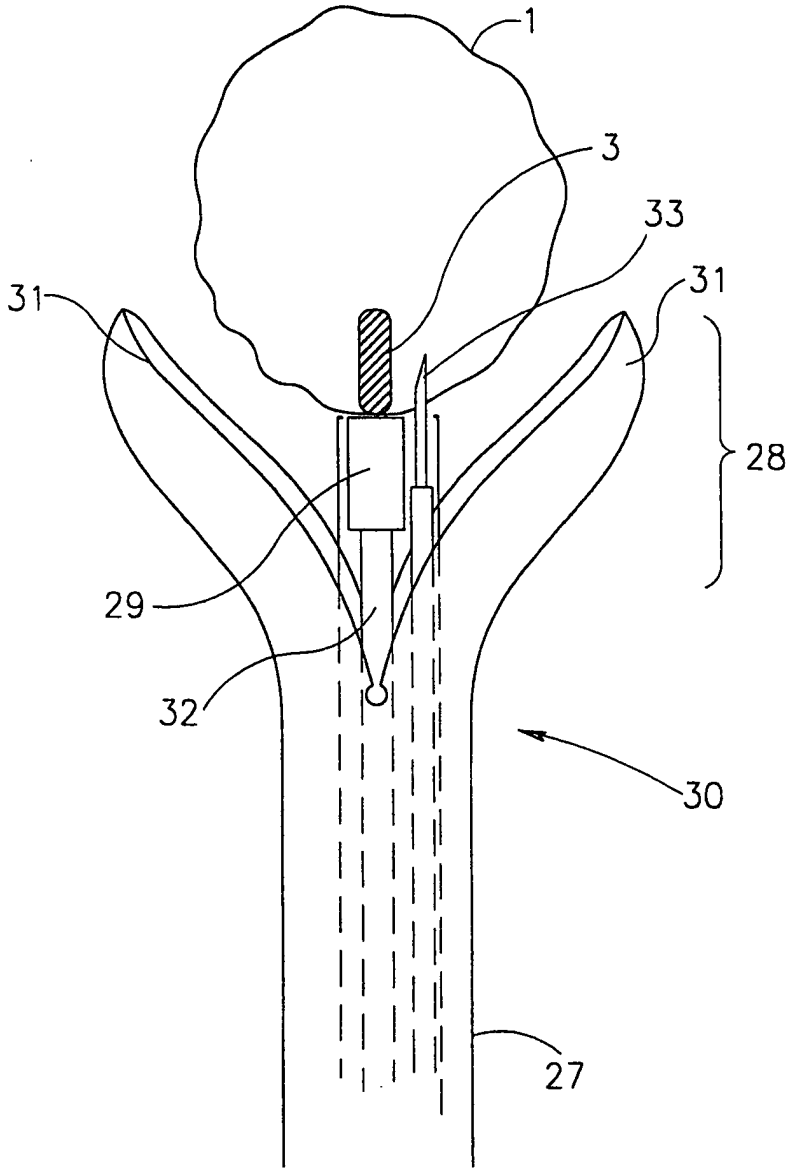


FIG.11

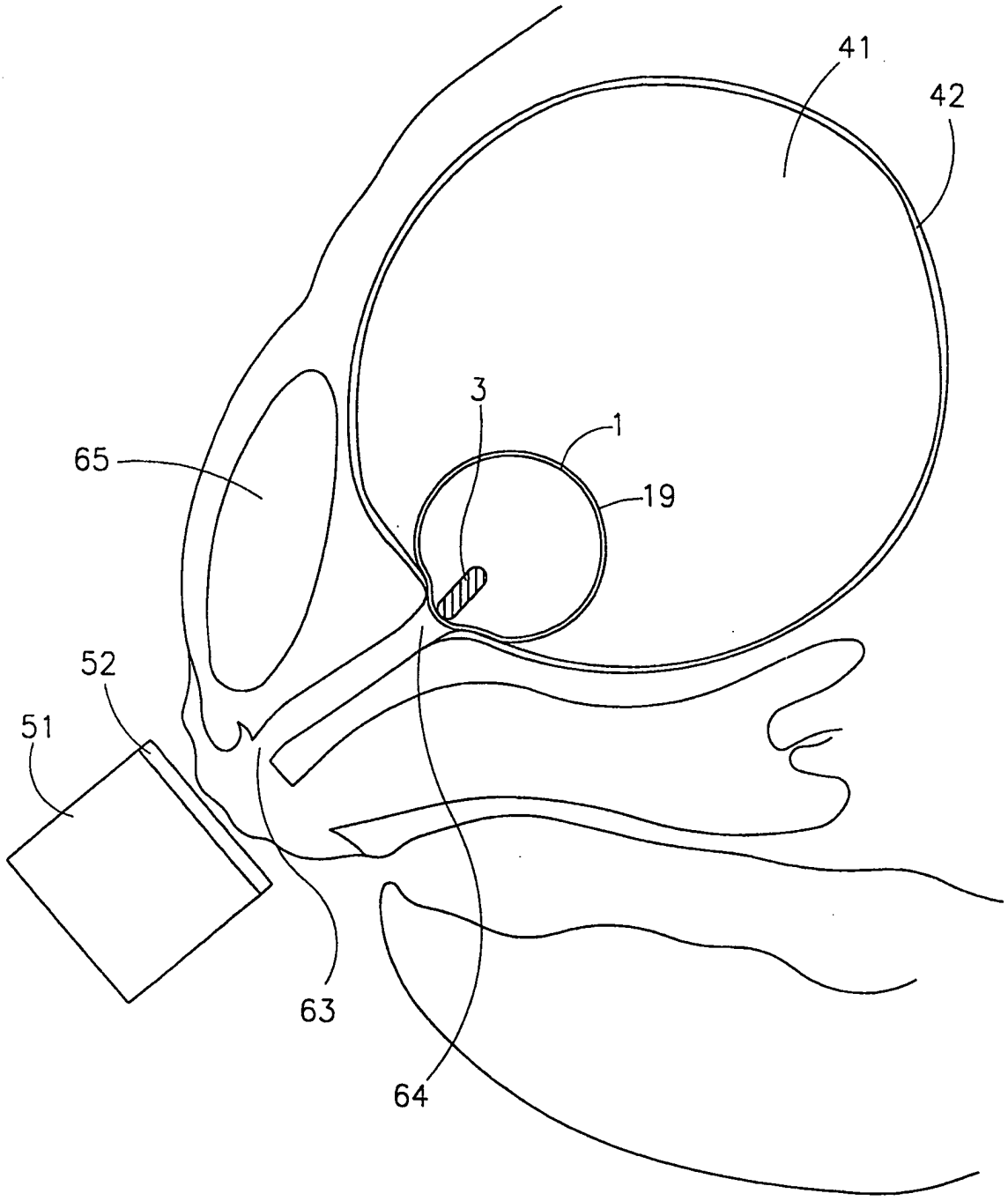


FIG.12

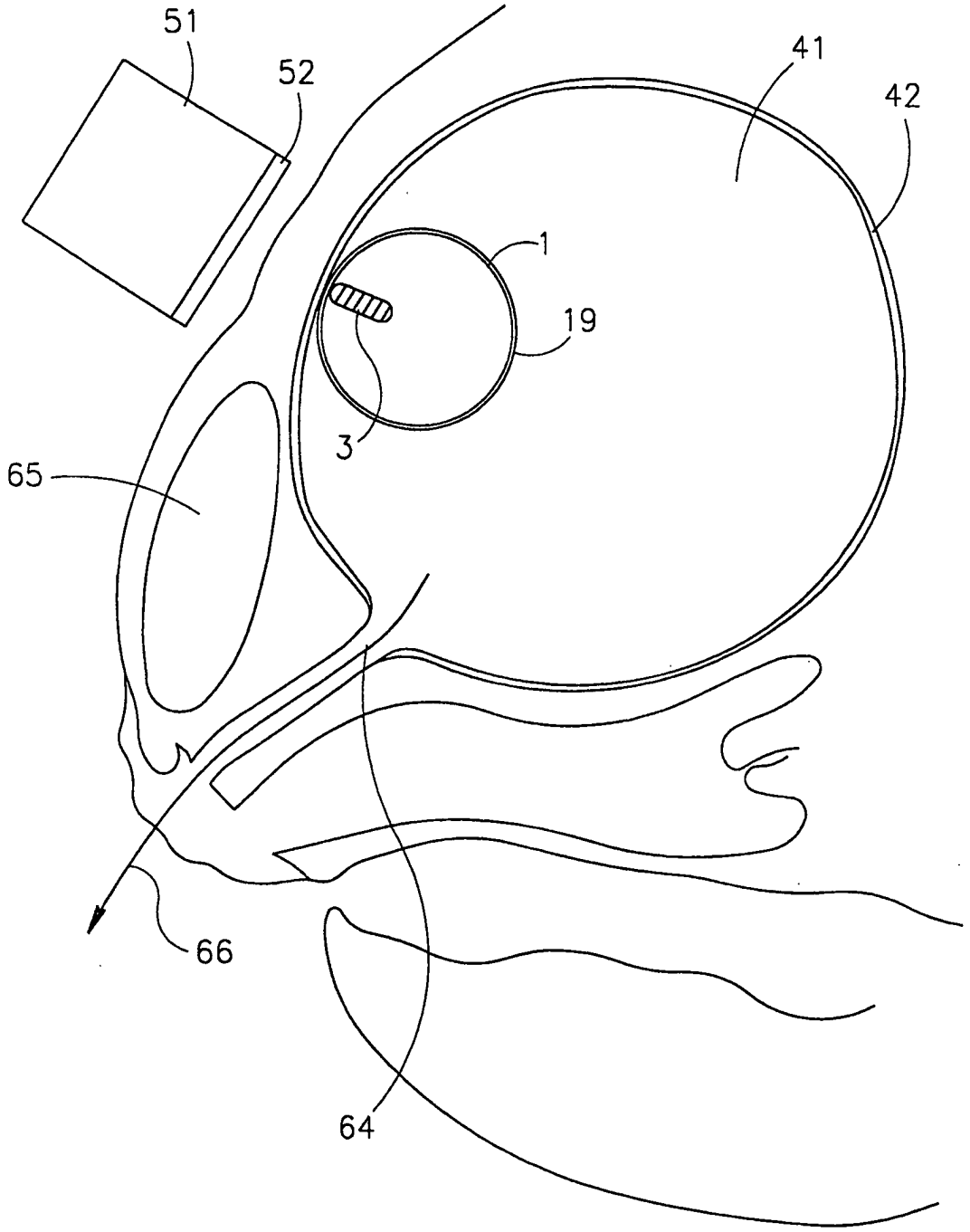


FIG.13

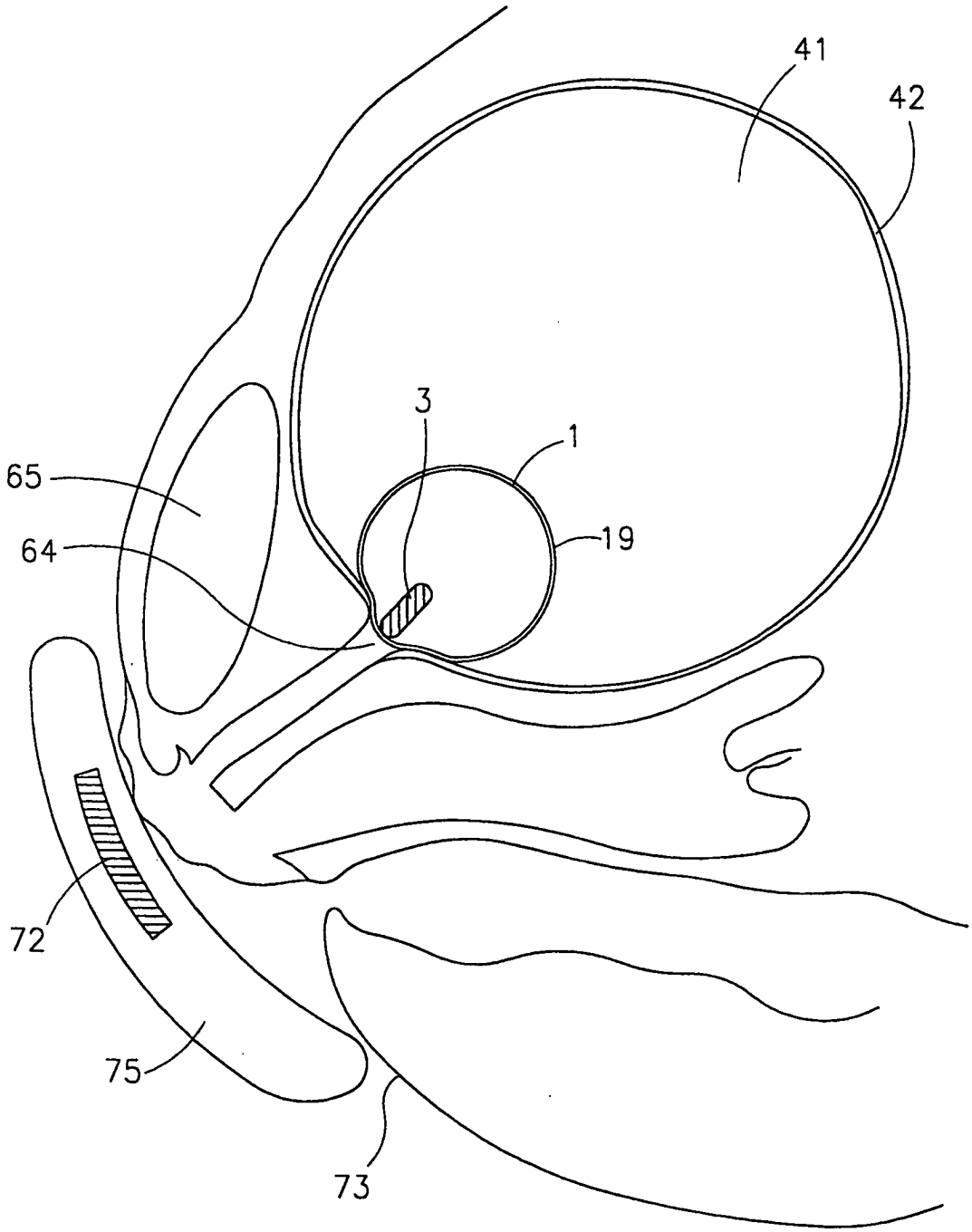


FIG.14

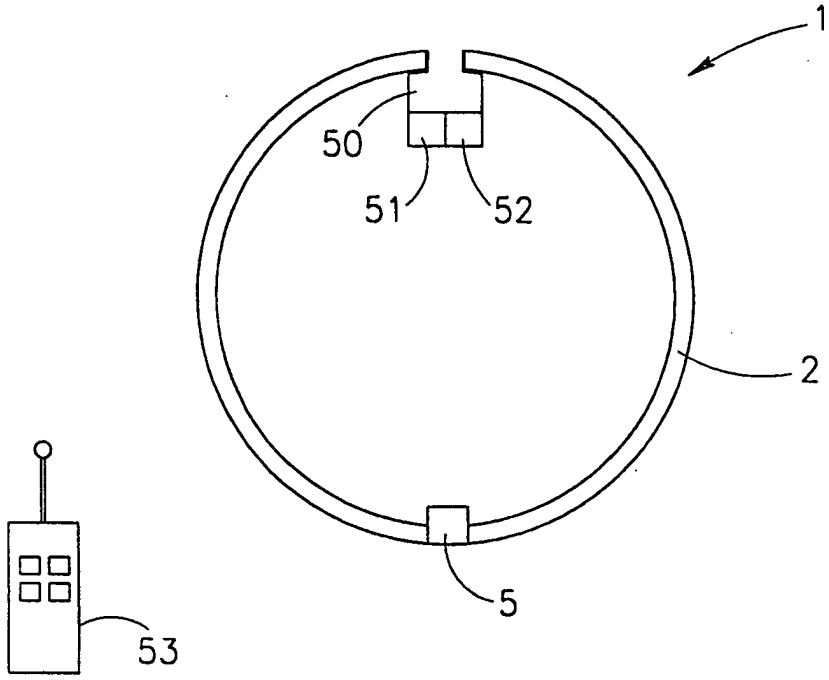


FIG.15

INTERNATIONAL SEARCH REPORT

Interna. .al Application No
PCT/IL 00/00160

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61F2/00 A61M31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61F A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 850 963 A (SPARKS ET AL) 25 July 1989 (1989-07-25) cited in the application the whole document	1,41
A	US 4 871 542 A (VILHARDT) 3 October 1989 (1989-10-03) the whole document	1,41

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 July 2000	10/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Smith, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna al Application No
PCT/IL 00/00160

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4850963 A	25-07-1989	AU 612692 B	18-07-1991
		AU 2177388 A	09-11-1989
		JP 1285263 A	16-11-1989
		EP 0357846 A	14-03-1990
US 4871542 A	03-10-1989	AU 622877 B	30-04-1992
		AU 2685088 A	02-08-1990
		EP 0372137 A	13-06-1990
		IN 168149 A	09-02-1991

(19)日本国特許庁（ＪＰ）　(12)公表特許公報（Ａ）　(11)特許出願公表番号
特表2000－513725
（P2000－513725A）
(43)公表日　平成12年10月17日(2000.10.17)

(51)Int.Cl.[7]	識別記号	ＦＩ	ﾃｰﾏｺｰﾄﾞ(参考)
Ａ６１Ｋ　9/00		Ａ６１Ｋ　9/00	
9/52		9/52	

審査請求　未請求　予備審査請求　有　（全 38 頁）

(21)出願番号　特願平10－504460
(86)(22)出願日　平成９年７月２日(1997.7.2)
(85)翻訳文提出日　平成10年12月29日(1998.12.29)
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(54)【発明の名称】　マイクロチップ薬物送達デバイス

(57)【要約】
多数の化学物質の放出の速度および時間の両方を制御し、そして送達されるべき薬物または持続様式または脈動様式のいずれかで広範な種々の分子の放出を可能にするマイクロチップが提供される。好ましい実施態様の全てにおいて、薬物もしくは他の分子および周囲液に不透過性である材料が基板として用いられる。リザーバは、マイクロ製造の分野において周知の化学（湿潤）エッチング技術またはイオンビーム（乾燥）エッチング技術のいずれかを用いて基板にエッチングされる。数百から数千のリザーバが、これらの技術を用いて１つのマイクロチップで製造され得る。放出システム（送達される分子を含む）は、注入、インクジェットプリント、またはスピンコーティング法によりリザーバに挿入される。例示の放出システムは、ポリマーおよびポリマー性マトリクス、非ポリマー性マトリクス、ならびに他の賦形剤または希釈液を含む。放出システムの物理学的特性は、分子の放出速度を制御する。リザーバは、多数の薬物または他の分子を種々の投与量で含み得る。充填されたリザーバは、経時的に分子を分解、溶解、またはリザーバから受動的に拡散させるかのいずれかを行う材料、あるいは電位の印加の際に酸化して、周囲液に溶解する可溶性化合物またはイオンを形成する材料でキャップされ得る。能動デバイスからの放出は、予めプログラムされたマイクロプロセッサ、リモートコントロール、またはバイオセンサにより制御され得る。

【特許請求の範囲】

１．分子の放出のためのマイクロチップデバイスであって、

基板および

該基板中の複数のリザーバを備え、ここで該リザーバがその中に組み込まれている分子を制御可能に放出する、マイクロチップデバイス。

２．前記リザーバが、異なるタイプの分子、異なる量の分子、またはそれらの組合せを含む、請求項１に記載のデバイス。

３．前記分子の放出が、前記リザーバ中に分子を組み込む放出システムにより制御される、請求項１に記載のデバイス。

４．前記放出システムの上の前記リザーバ上に位置した分解性リザーバキャップをさらに備え、ここで前記キャップの分解速度が分子が該リザーバから放出される時間を決定する、請求項３に記載のデバイス。

５．前記リザーバキャップが異なる厚さを有する、請求項４に記載のデバイス。

６．前記リザーバキャップが分解または溶解された後、リザーバ中の前記放出システムが分解または溶解し、前記分子を放出する、請求項４に記載のデバイス。

７．脈動放出が、１つのリザーバ中に異なる放出システムおよびリザーバキャップ材料を重層することにより、該リザーバから得られる、請求項４に記載のデバイス。

８．前記放出システムが非分解性であり、そして前記分子の該放出システムからの拡散が、前記リザーバキャップの分解後に該分子の脈動放出を提供する、請求項４に記載のデバイス。

９．放出システムの上のリザーバ上に位置した非分解性リザーバキャップをさらに備え、前記分子のキャップを通じる拡散速度が、分子がリザーバから放出される速度を決定する、請求項３に記載のデバイス。

１０．カソード、マイクロプロセッサ、タイマー、デマルチプレクサ、および電源をさらに備え、ここで該リザーバキャップがアノードであり、そしてそれぞれ該カソードの１つによって囲まれ、ここで各カソードとアノードとの間の電位の印加の際に、該リザーバキャップが酸化し、溶液中に溶解し、そして下にある放

出システムを周囲液に露出する、請求項４に記載のデバイス。

１１．前記マイクロプロセッサ機能が、特定の時間で個々のリザーバの電極を活性化させるように予めプログラムされたメモリソースにより指示される、請求項１０に記載のデバイス。

１２．前記マイクロプロセッサ機能が、各リザーバの電極を活性化させるようにリモートコントロールにより指示される、請求項１０に記載のデバイス。

１３．バイオセンサをさらに備え、ここで前記マイクロプロセッサ機能が、各リザーバの電極を活性化するように該バイオセンサにより指示される、請求項１０に記載のデバイス。

１４．前記放出システムが賦形剤または希釈剤中に薬物分子を含む、請求項２に記載のデバイス。

１５．各リザーバ中の前記放出システムが、放出される分子で形成され、ここで該分子の溶解速度が該分子の放出速度を決定する、請求項１４に記載のデバイス。

１６．分子の放出のためのデバイスを製造する方法であって、

基板を提供する工程；

エッチマスクとして使用するために、該基板上に絶縁性材料を堆積させ、そしてパターニングする工程；

該基板中に複数のリザーバをエッチングする工程；

該リザーバに放出システムおよびキャップ材料を充填する工程；および

放出システムおよびキャップ材料をエッチングする工程

を包含する、方法。

１７．前記リザーバの上の絶縁性材料の薄いフィルムを取り除く工程をさらに包含する、請求項１６に記載の方法。

１８．各リザーバを、異なるタイプおよび量のキャップ材料および、送達される分子を含む放出システムで充填する工程をさらに包含する、請求項１６に記載の方法。

１９．前記リザーバが、注入、インクジェットプリント、またはスピンコーティ

ングによって充填される、請求項１６に記載の方法。

２０．前記リザーバが、インクジェットプリントによって充填される、請求項１９に記載の方法。

２１．各リザーバの上の絶縁性材料の薄いフィルムの上に誘電性材料の薄いフィルムをを堆積させる工程をさらに包含する、請求項１７に記載の方法。

２２．アノードが各開口部を被覆し、そしてカソードが各アノードの周囲にあるように、誘電性フィルムを電極にパターニングする工程をさらに包含する、請求項２１に記載の方法。

２３．前記アノードが直に前記リザーバの上にあり、そして前記カソードが各アノードの露出された部分の周囲にあることを除いて、各電極の上に材料を堆積させる工程をさらに包含する、請求項２２に記載の方法。

２４．分子の送達のための方法であって、

分子が送達されるべき部位に、基板および該基板中の複数のリザーバを含む、分子の放出のためのマイクロチップデバイスを提供する工程であって、ここで該リザーバがその中に組み込まれている分子を制御可能に放出する、工程

を包含する、方法。

２５．前記分子が薬物であり、前記マイクロチップを患者に投与するか、移植するか、または注入することを包含する、請求項２４に記載の方法。

２６．前記分子が、核酸、タンパク質、アミノ酸、多糖類、および有機分子または合成分子からなる群から選択される薬物である、請求項２５に記載の方法。

２７．前記薬物が、薬学的に受容可能なキャリアと組み合わされている、請求項２６に記載の方法。

２８．前記分子が診断試薬または化学試薬である、請求項２４に記載の方法。

２９．前記分子が、脈動様式または持続様式で放出される、請求項２４に記載の方法。

３０．前記放出システムが、放出される分子により形成されている、請求項２４に記載の方法。

３１．分解性リザーバキャップが、前記放出システムの上のリザーバ上に位置し

、ここで前記キャップの分解、溶解、または拡散速度が、前記分子が該リザーバから放出される時間を決定する、請求項２４に記載の方法。

３２．前記デバイスが、カソード、マイクロプロセッサ、タイマー、デマルチプレクサ、および電源をさらに備え、前記リザーバキャップがアノードであり、そしてそれぞれ該カソードの１つにより囲まれ、ここで前記方法が、各カソードとアノードとの間で電位を印加して、該リザーバキャップを酸化し、そして下にある放出システムを周囲液に露出する工程を包含する、請求項２４に記載の方法。

３３．前記マイクロプロセッサ機能が、特定の時間で個々のリザーバの電極を活性化させるようにプログラムされたメモリソースにより指示され、ここで前記方法が該メモリをプログラムする工程を包含する、請求項３２に記載の方法。

３４．前記マイクロプロセッサ機能が、各リザーバの電極を活性化させるようにリモートコントロールにより指示される、請求項３２に記載の方法。

３５．前記デバイスがバイオセンサをさらに備え、ここで前記マイクロプロセッサ機能が、各リザーバの電極を活性化するように該バイオセンサにより指示される、請求項３２に記載の方法。

【発明の詳細な説明】

マイクロチップ薬物送達デバイス

発明の背景

本発明は、小型化薬物送達デバイスに関し、そしてより詳細には、制御された時間および速度放出マルチウェル化薬物送達デバイスに関する。

薬物送達は、医療処置の重要な局面である。多くの薬物の効力は、それらが投与される経路に直接関連している。いくつかの療法は、薬物が長期間にわたって患者に繰り返し投与されることを必要とする。このことは、適切な薬物送達方法の選択において問題となる。患者はしばしば医薬を服用することを忘れたり、気が向かなかったり、またはできなかったりする。薬物送達はまた、薬物が全身送達には強すぎる場合、問題となる。従って、薬物および他の治療薬を包含するがこれらに限定されない広範な種々の分子の制御された放出、脈動的な放出、または持続した放出を可能にする送達デバイスを設計および製造する試みが行われている。

制御放出ポリマーデバイスは、患者への投与後所望の期間にわたるポリマーからの薬物の拡散および／またはポリマーの分解により、ある期間にわたる薬物放出を提供するように設計されている。しかし、これらのデバイスは、比較的単純である。

Cimaらの米国特許第5,490,962号は、所望の時間枠にわたる１つ以上の薬物の放出を提供するより複雑なデバイスを製造するために、三次元プリンティング法の使用を開示している。複雑なデバイスを製造するための一般的な手順が記載されているが、特定の設計は詳述されていない。

Ellinwoodの米国特許第4,003,379号は、可撓性の格納式の壁を有する容器を備える移植可能な、電気機械駆動デバイスを記載している。このデバイスは、注入口を介して貯蔵域から医薬を受容し、次いで注出口を介して体内に医薬を分与する。Ellinwoodの米国特許第4,146,029号および米国特許第3,692,027号は、プログラム可能な小型化分与手段を有する自家動力投薬システムを開示している。Jassawallaの米国特許第4,360,019号は、カテーテルを通じた薬物の送達のための

作動手段を備える移植可能な注入デバイスを開示している。作動手段は、ソレノイド駆動小型ポンプを備える。これらのデバイスの全ては、体内で作用するのに必要な小型出力駆動機械部（すなわち、それらが引っ込むか、分与するか、または押し出す）を備える。これらは複雑であり、そして壊れやすい。さらに、複雑さおよびサイズの制限のために、それらは、一度に数種より多くの薬物または薬物混合物を送達するのに不適切である。

従って、本発明の目的は、一度に数週間または数年の間作用し得る薬物および他の分子のための分与可能なマルチウェル化送達デバイスの簡便な使用および製造を提供することである。

本発明の別の目的は、脈動様式または持続様式のいずれかでの薬物または他の分子の送達を可能にするこのようなデバイスを提供することである。

本発明のさらに別の目的は、送達が受動または能動のいずれかで制御されることを可能にするこのようなデバイスを提供することである。

本発明の目的はまた、種々の投与量の多くの異なる薬物または他の分子を保持し得、そして所望ならば、移植、注入、または飲み込まれるのに十分に小さいこのようなデバイスを提供することである。

発明の要旨

広範な種々の分子の送達のためのマイクロチップが提供される。マイクロチップは、集積回路の製造に一般に適用される方法（例えば、紫外線(UV)フォトリソグラフィー、リアクティブイオンエッチング、および電子ビームエバポレーション）を用いて構築された小型化デバイスである。マイクロチップは、分子が放出される速度ならびに放出が開始する時間について制御を提供する。放出の時間は、受動的または能動的に制御され得る。

好ましい実施態様では、周囲液(surrounding fluid)および送達されるべき分子に不透過性である材料が基板として使用される。基板材料の例は、セラミクス、半導体（例えば、シリコン）、および分解性および非分解性ポリマーである。リザーバは、マイクロ製造の分野において一般に用いられる化学（湿潤）エッチング技術またはイオンビーム（乾燥）エッチング技術のいずれかを用いて基板にエ

ッチングされる。数百から数千のリザーバが、これらの技術を用いて１つのマイクロチップで製造され得る。代表的には、送達される分子を含むか、カプセル化するか、または分子からなる放出システムは、注入、インクジェットプリント、または他の手段によりリザーバに挿入される。放出システムは、分子の放出速度を制御する。放出速度は、放出システムの組成および構造の関数である。デバイス設計により、リザーバに、固体、液体、またはゲル形態で放出システムを充填することが可能になる。１つのマイクロチップのリザーバのそれぞれは、異なる分子および／または異なる量および濃度を含み得、これらは独立して放出され得る。

好ましい実施態様では、リザーバキャップは、電源を必要としない、分子の受動的な定時放出(timed release)を可能にする。リザーバは、送達される分子について既知の速度で分解または溶解する材料、または既知の透過性（拡散定数）を有する材料でキャップされる。従って、キャップ材料の分解、溶解、または拡散特性は、特定のリザーバ中で分子の放出が開始する時間を決定する。実際は、マイクロチップは、放出システム（速度コントローラ）の選択およびキャップ材料（タイムコントローラ、およびいくつかの場合では速度コントローラ）の選択による、分子の放出の二重制御を提供する。

別の好ましい実施態様では、リザーバキャップは、電源を必要とする、分子の能動的な定時放出を可能にする。この実施態様では、リザーバキャップは、リザーバの上に堆積され、所望の幾何学にパターニングされ、そしてアノードとして働く誘電性材料の薄いフィルムからなる。カソードもまた、デバイスの適用および電位制御方法に依存するそれらの大きさおよび堆積を有するデバイス上で製造される。溶液中に溶解し得るか、または電位の印加の際に可溶性化合物またはイオンを形成し得る誘電性材料（金属（例えば、銅、金、銀、および亜鉛）およびいくつかのポリマーを含む）が、能動定時放出デバイスにおいて用いられる。アノードとカソードとの間に電位が印加される場合、リザーバの上方のアノードの誘電性材料が酸化して、溶液中に溶解する可溶性化合物またはイオンを形成し、送達される分子を含む放出システムを周囲液に露出する。あるいは、電位の印加は、アノードリザーバキャップ付近の局所的なｐＨの変化を生じさせ、通常不溶

性のイオンまたは酸化生成物を可溶性にするために用いられ得る。このことにより、リザーバが溶解し、そして送達システムを周囲液に露出させる。いずれの場合においても、送達される分子は、放出システムからの拡散または放出システムの分解もしくは分離によって、周囲液に放出される。放出の頻度は、マイクロチップ上に小型化電源およびマイクロプロセッサを取り付けることによって制御される。任意のリザーバの活性化は、マイクロプロセッサの予備プログラミング、リモートコントロール、またはバイオセンサからの信号によって達成され得る。

図面の簡単な説明

図１は、受動送達デバイスのための代表的な製造スキームを示す。

図２は、能動送達デバイスのための代表的な製造スキームを示す。

図３は、代表的なデバイス制御回路フローシートを示す。

図４は、受動送達デバイスを示す。

図５は、能動送達デバイスを示す。

図６は、絶縁体オーバーレイヤを含む能動デバイスを示す。

図７ａ－ｉは、受動送達デバイスのいくつかの堆積の模式図である。

図８ａ－ｃは、能動送達デバイスのいくつかの堆積の模式図である。

発明の詳細な説明

患者または他の実験システムの必要性に従って規定された速度および時間で薬物および他の分子を正確に送達し得るマイクロチップデバイスが、提供される。本明細書中で使用される「マイクロチップ」は、例えば以下によって記載されるような、紫外線（UV）、フォトリソグラフィー、リアクティブイオンエッチング、および電子ビームエバポレーションのような集積回路の製造に一般的に適用される方法を使用して構成された小型化デバイスである：例えば、S. WolfおよびR.N. Tauber, Silicon Processing for the VLSI Era, 第１巻－Process Technology, Lattice Press, Sunset Beach, CA, 1986;およびR.C. Jaeger, Introduction to Microelectronic Fabrication, 第Ｖ巻, Modular Series on Solid State Devices, Addison-Wesley, Reading, MA, 1988。マイクロチップは、分子が放出さ

れる速度および放出が開始する時間の制御を提供する。放出時間は、受動的または能動的に制御され得る。マイクロチップの製造の手順は、数ミリメートルから数センチメートルまでの範囲の基本的な寸法（四角形もしくは方形である場合は側部の長さ、または円形である場合は直径）を有するデバイスの製造を可能にする。代表的なデバイスの厚さは、300μｍである。しかし、デバイスの厚さは、約10μｍから数ミリメートルまでで変化し得る。デバイスの厚さの変化は、マイクロチップに組み込まれ得るリザーバの最大数、および各リザーバの容積に影響を与える。デバイスのインビボの適用は、代表的には、２㎝以下の一次元の寸法を有するデバイスを必要とする。インビボの適用のためのデバイスは、最小の侵襲手順を使用して飲み込まれるか、または移植されるに十分に小さい。より小さいインビボのデバイスが（およそ１ミリメートル）が、カテーテルまたは他の注射可能な手段を使用して移植され得る。インビトロの適用のためのデバイスは、より少ない大きさの制限を有し、そして必要であれば、インビボのデバイスの寸法の範囲よりもはるかに大きく作製され得る。

デバイス製造のための材料

各デバイスは、基板、リザーバ、および送達される分子を含む、囲む、または層状にされた放出システムから構成される。分子の放出時間を制御するデバイスは、リザーバキャップを含み得る。能動なデバイスは、制御回路および電源を含み得る。

基板

基板は、エッチングされたか（etched）または機械加工されたリザーバを含み、これはマイクロチップの支持体として作用する。支持体として作用し得るエッチングまたは機械加工に適切であり、そして送達される分子および周辺を取りまく液体（例えば、水、血液、電解質、'または他の溶液）に対して不浸透性である任意の材料が基板として使用され得る。基板の材料の生体適合性が好ましいが、必要ではない。インビボの適用について、使用の前に、非生体適合性材料が生体適合性材料（例えば、ポリ（エチレングリコール）またはポリテトラフルオロエチ

レン様材料）中にカプセル化され得る。送達される分子に不浸透性であり、そして液体で取り囲まれている、強力な、非分解性の、容易にエッチングされる基板の一例は、シリコンである。別の実施態様において、基板は、生体適合性成分中でのある期間を超えると分解するかまたは溶解する頑丈な材料から作製される。この実施態様は、デバイスが移植され、そして後の時点でのデバイスの物理的な除去が不可能であるかまたは薦められないインビボでの適用（例えば、脳の移植）に好ましい。頑丈な生体適合性の材料のクラスの例は、K.E. Uhrichら、「Synthesis and characterization of degradable poly(anhydride-co-imides)」、Macromolecules, 1995, 28, 2184-93によって議論されるポリ（無水物-co-イミド）である。

放出システム

送達される分子は、それらの純粋な形態で（液体の溶液、またはゲルとして）リザーバに挿入され得るか、またはそれらは、放出システム内または放出システムによってカプセル化され得る。本明細書中で使用される「放出システム」は、分子が固体もしくは液体のいずれかとして純粋な形態で存在するか、あるいは分解性材料またはマトリックスの拡散もしくはマトリックスの崩壊によって取り込まれた分子を放出する材料で形成されるマトリックス中に存在する両方の状況を含む。分子は、放出システムにしばしば含まれ得る。なぜなら、放出システムの分解、溶解、分散特性が分子の放出速度を制御するための方法を提供するからである。分子は、放出システム内に均一または不均一に分布し得る。放出システムの選択は、所望される分子の放出速度に依存する。非分解性放出システムおよび分解性放出システムの両方が、分子の送達に使用され得る。適切な放出システムとして、ポリマーおよびポリマー性マトリックス、非ポリマー性マトリックス、または無機および有機の賦形剤ならびに希釈物（例えば、炭酸カルシウム、およびショ糖、しかし、これらに限定されない）が挙げられる。放出システムは、天然または合成であり得るが、放出プロフィールの良好な特徴のために合成の放出システムが好ましい。放出システムは、放出が所望される期間に基づいて選択される。対照的に、数秒のように短い放出時間が、いくつかのインビボの適用に所

望され得る。いくつかの場合において、リザーバからの持続（一定）放出が最も有用であり得る。他の場合において、リザーバからのパルス（バルク）放出がより有効な結果を提供し得る。１つのリザーバからの１回のパルスが複数のリザーバを使用することによる脈動放出に転換され得ることに留意すること。放出システムのいくつかの層および他の材料を単一のリザーバに組み込んで単一のリザーバからの脈動送達を達成することもまた可能である。持続放出は、分解するか、溶解するか、または長時間にわたってそれを通って分子の分散を可能にする放出システムを組み込むことによって達成され得る。さらに、持続放出は、迅速に連続する数回の分子のパルスを放出することによって、刺激され得る。

放出システム材料は、種々の分子量の分子が、材料からもしくは材料による分散によるか、または材料の分解によってリザーバから放出されるように選択され得る。生分解性ポリマー、生体侵食性ヒドロゲル、およびタンパク質送達システムが、分散、分解、または溶解による分子の放出に好ましい。一般に、これらの材料は、酵素的加水分解またはインビボもしくはインビトロでの水への露出によって、あるいは表面または多量の侵食によってのいずれかで、分解または溶解する。代表的な合成の生分解性ポリマーとして、以下が挙げられる：ポリ（アミノ酸）およびポリ（ペプチド）のようなポリ（アミド）；ポリ（乳酸）、ポリ（グリコール酸）、ポリ（乳酸-CO-グリコール酸）、およびポリ（カプロラクトン）のようなポリ（エステル）；ポリ（無水物）；ポリ（オルトエステル）；ポリ（カーボネート）；ならびにそれらの化学的誘導体（置換体、化学基の付加（例えば、アルキル、アルキレン、ヒドロキシル化、酸化）および当業者によって日常的に作製される他の改変体）、コポリマー、ならびにそれらの混合物。

代表的な合成の非生分解性ポリマーとして、以下が挙げられる：ポリ（エチレンオキシド）、ポリ（エチレングリコール）、およびポリ（テトラメチレンオキシド）のようなポリ（エーテル）；ビニルポリマーーポリ（アクリレート）およびポリ（メタクリレート）（例えば、メチル、エチル、他のアルキル、ヒドロキシエチル、メタクリレート、アクリル酸およびメタクリル酸、ならびにポリ（ビニルアルコール）、ポリ（ビニルピロリドン）、およびポリ（ビニルアセテート）のような他のもの）；ポリ（ウレタン）；セルロースおよびその誘導体（例

えば、アルキル、ヒドロキシアルキル、エーテル、エステル、ニトロセルロース、および種々のセルロースアセテート）；ポリ（シロキサン）；ならびにそれらの任意の化学的誘導体（置換体、化学基の付加（例えば、アルキル、アルキレン、ヒドロキシル化、酸化）および当業者によって日常的に作製される他の改変体）、コポリマー、ならびにそれらの混合物。

放出される分子

任意の天然もしくは合成の、有機分子もしくは無機分子、またはその混合物が送達され得る。１つの実施態様において、マイクロチップが薬物をそれを必要とする患者に全身的に送達するために用いられる。別の実施態様において、患者におけるマイクロチップの構築および配置は、全身的な送達には強力すぎ得る薬物の局在化した放出を可能にする。本明細書中で使用される場合、薬物は、生物活性効果を有する有機または無機分子（タンパク質、核酸および合成有機分子を包含する）であり、例えば、麻酔薬、ワクチン、化学療法剤、ホルモン、代謝物、糖、免疫調節因子、抗酸化剤、イオンチャンネル調節因子、および抗生物質を含む。薬物は、単一の薬物または薬物の混合物の形態であり得、そして薬学的に受容可能なキャリアを含み得る。別の実施態様において、分子は、例えば、分析化学または医学的診断の分野において少量（ミリグラム～ナノグラム）の１つ以上の分子の制御された放出が必要とされる任意のシステムにおいて、インビトロで放出される。分子は、pH緩衝剤、診断剤、およびポリメラーゼ連鎖反応または他の核酸増幅手順のような複雑な反応における試薬として有効であり得る。

リザーバキャップ

受動的な定時放出薬物送達デバイスにおいて、リザーバキャップは、経時的に分解もしくは溶解する材料、または分解や溶解はしないが送達される分子に対して透過性である材料から形成される。これらの材料は、好ましくはポリマー材料である。材料は、異なるリザーバから異なる時間に、いくつかの場合には、異なる速度で分子を放出し得るように、種々の分解速度または溶解速度または透過性を与えるためのリザーバキャップとしての使用のために選択され得る。異なる放出時間（放出時間遅延の量）を得るために、キャップが異なるポリマー、異なる

架橋の程度を有する同じポリマー、またはUV重合可能ポリマーで形成され得る。後者の場合、このポリマーのUV光への露出を変えることによって、種々の程度の架橋を生じ、そしてキャップ材料に異なる拡散特性または分解もしくは溶解速度を与える。異なる放出時間を得るための別の方法は、１つのポリマーを用いてではあるが、そのポリマーの厚さを変える。いくつかのポリマーのより厚いフィルムは、遅延した放出時間を生じる。ポリマーの任意の組合せ、架橋の程度、またはポリマーの厚さは、特定の放出時間または速度を得るために改変し得る。１つの実施態様において、送達されるべき分子を含有する放出システムは、分子にとってほとんど不透過性である分解可能なキャップ材料によって覆われる。リザーバからの分子の放出時間は、キャップ材料が分解または溶解するために必要な時間によって制限される。別の実施態様において、キャップ材料は、非分解性であり、そして送達される分子に対して透過性である。使用される材料の物理的な特性、その架橋の程度、およびその厚さは、キャップ材料を通して拡散する分子に必要とされる時間を決定する。放出システムからの拡散が制限される場合、キャップ材料は、放出の開始を遅延させる。キャップ材料からの拡散が制限される場合、キャップ材料は、分子の放出速度ならびに放出の開始の遅延を決定する。

能動定時放出デバイスにおいて、リザーバキャップは、リザーバの上に堆積した、所望の幾何学にパターニングされた、そしてアノードとして作用する誘電性材料の薄いフィルムからなる。カソードはまた、そのサイズおよび配置がデバイスの適用および電位制御の方法に依存するデバイス上に作製される。アノードは、酸化が起こる電極として規定される。溶液中に溶解し得るか、または電位の適用に際して可溶性のイオンもしくは酸化化合物を形成し得る任意の誘導性材料が、アノードおよびカソードの作製のために使用され得る。さらに、電位に応答して不溶性のイオンまたは酸化生成物を通常形成する材料は、例えば、アノード付近での局所的なpH変化がこれらの酸化生成物が可溶性になるようにする場合、使用され得る。適切なリザーバキャップ材料の例には、銅、金、銀、および亜鉛、ならびに例えば、I.C. Kwonら「Electrically erodible polymer gel for controlled release of drugs」、Nature, 1991, 354, 291-93;およびY.H. Baeら、「Pu

lsatile drug release by electric stimulus」、ACS Symposium Series, 1994, 545, 98-110に記載されるいくつかのポリマーが含まれる。

デバイスパッケージング、制御回路、および電源

マイクロエレクトロニックデバイスパッケージは、代表的には、酸化アルミニウムまたは窒化シリコンのような絶縁性材料または誘電性材料から作製される。これらの目的は、デバイスの全ての構成要素が密接に配置されることを可能にし、そして電源および互いへの構成要素の相互連結を容易にすることである。送達デバイスのインビボ適用のために、全パッケージング（全ての構成要素（すなわち、デバイス、マイクロプロセッサ、および電源）を含む）が、ポリ（エチレングリコール）またはポリテトラフルオロエチレン様材料のような生体適合性材料中にコートまたはカプセル化される。インビトロ適用のために必要とされる材料は、それほどストリンジェントでなくてもよく、そして特定の状況に依存する。

制御回路は、タイマー、デマルチプレクサ、マイクロプロセッサ、およびインプットソース（例えば、メモリソース、信号レシーバ、またはバイオセンサ）からなる。タイマーおよびデマルチプレクサ回路は、電極の作製の間にマイクロチップの表面上に直接設計および組み込まれ得る。マイクロプロセッサの選択のための基準は、小サイズ、低出力要求、およびメモリソース、信号レシーバ、またはバイオセンサからの出力をデマルチプレクサから送達デバイス上の特定のリザーバへの出力の方向のアドレスに翻訳する能力である。メモリソース、信号リザーバ、またはバイオセンサのようなマイクロプロセッサへの入力のソースの選択は、送達デバイスの特定の適用およびデバイスオペレーションが予めプログラムされ、リモート手段により制御され、またはその環境からのフィードバック（例えば、バイオフィードバック）により制御されているか否かに依存する。

電源の選択のための基準は、小サイズ、十分な出力能、制御回路に組み込まれる能力、再充電される能力、および再充電が必要とされるまでの時間の長さである。いくつかのリチウムベースの、再充電可能なマイクロ電池がS.D. JonesおよびJ.R. Akridge、「Development and performance of a rechargeable thin-film solid-state microbattery」、Journal of Power Sources, 1995, 54, 63-67;

およびJ.B. BAtesら、「New amorphous thin-film lithium electrolyte and rechargeable microbattery」、IEEE 35th International Power Sources Symposium, 1992, 337-39に記載されている。これらの電池は、代表的には、わずか厚さ10ミクロンであり、そして1cm²面積を占める。１つ以上のこれらの電池が送達デバイス上に直接組み込まれ得る。

デバイス製造の方法

リザーバの製造

デバイスは、当業者に公知の方法を用いて製造され、例えばWolfら(1986)；およびJaeger(1988)；Kwonら(1991)によって総説される。

図１および２に図示されるマイクロチップ製造（それぞれ、受動デバイスおよび能動デバイス）の好ましい方法において、製造は、材料、代表的には絶縁性または誘電性材料を、リザーバエッチングの間にエッチマスクとして作用するように基板上に堆積すること、およびフォトリソグラフィー的にパターニングすることによって始める。マスクとしての使用のための代表的な絶縁性材料は、窒化シリコン、シリコンジオキシド、およびポリイミドのようないくつかのポリマーを含む。好ましい実施態様において、無定形窒化シリコン(SiN_x)の薄いフィルム(約1000～3000Å)は、Plasma Enhanced Chemical Vapor Deposition(PECVD)によってシリコンウェハ30/300の両側面上に堆積される。あるいは、低応力のシリコン豊富な窒化物がVertical Tube Reactor (VTR)に堆積され得るか、または化学量論的多結晶窒化物が、Low Pressure Chemical Vapor Deposition(LPCVD)によって堆積され得る。リザーバは、紫外線フォトリソグラフィー、およびプラズマエッチング、または熱リン酸からなる化学的エッチングのいずれかによって、ウェハ32/320の一側面上の窒化シリコンフィルム中にパターニングされる。パターニングされた窒化シリコンは、濃縮された水酸化カリウム溶液（80～85℃の温度にて約38.5重量％）によって、露出されたシリコン34/340の化学的エッチング用のエッチマスクとし作用する。あるいは、リザーバは、リアクティブイオンエッチングまたはイオンビームエッチングのような、乾燥エッチング技術によって、基板中においてエッチングされ得る。これらの技術は、例えばWolfら(1986)およ

びJaeger(1988)によって総説されるように、マイクロエレクトロニックデバイスの製造において通常使用される。これらのマイクロ製造技術の使用は、単一のマイクロチップ上への数百から数千のリザーバの組込みを可能にする。受動デバイスにおいて、リザーバは、１μｍほど小さく離れ得る。能動デバイスにおいて、リザーバ間の距離は、各リザーバ上またはその近傍の電極によって占められる空間に起因して、わずかに大きく(約10～15μｍ)あり得る。リザーバは、ほとんど任意の形状および深さに作製され得、そして基板を完全に貫通する必要はない。好ましい実施態様において、水酸化カリウムによってシリコン基板（100）中にエッチングされたリザーバは、54°でのスロープの側面壁を有する方形ピラミッドの形状にあり、そして基板（約300μｍ）を完全に通って基板の他方の側面上の窒化シリコンフィルムに達し、SiN_4膜を形成する。（ここで、窒化シリコンフィルムは、水酸化カリウムエッチングストップとして作用する。）ピラミッド形状は、基板のパターニングされた側面上のリザーバ(約500μｍ×500μｍ)の大きな開口を通るリザーバの容易な充填を可能にし、基板の他方の側面上のリザーバ（約30μｍ×30μｍ）の小さな開口を通って放出し、そして送達される薬物または他の分子を貯蔵するためのデバイスの内側に大きな空胴を提供する。

受動定時放出リザーバキャップの製造

受動定時放出マイクロチップの製造において、リザーバキャップ材料は、微量注射器36aで注入されるか、インクジェットプリンターカートリッジでプリントされるか、またはリザーバの小さな開口上になお存在する絶縁性マスク材料の薄いフィルムを有するリザーバ中にスピンコーティング36bされる。注入またはインクジェットプリント方法が使用される場合、キャップ形成は、材料がリザーバ38a中に注入されるかまたはプリントされた後、完全であり、そしてさらなる処理を必要としない。スピンコーティングが使用される場合、キャップ材料は、複数のスピンコーティング36bによってプラナライズ(planarize)される。次いで、フィルムの表面は、プラズマ、イオンビーム、または化学的エッチング液によって、所望のキャップ厚さが得られるまで38bエッチングされる。好ましい実施態様において、使用される絶縁性材料は、窒化シリコンであり、そしてキャップ材

料は、キャップ材料の溶液で充填されるインクジェットカートリッジで、リザーバ中にプリントされる。

リザーバキャップは、分子がリザーバから放出される時間を制御する。各リザーバキャップは、異なる厚さであり得るか、または異なる物理的性質を有し得、分子を含む各放出システムが、周囲液に露出される時間を変化させ得る。注入、インクジェットプリント、およびスピンコーティングは、リザーバ充填の好ましい方法であり、そして任意のこれらの方法は、リザーバの形状またはサイズにかかわらず、リザーバを充填するために使用され得る。しかし、注入およびインクジェットプリントは、深い（10μmより深い）リザーバまたは大きな開口（100μmより大きい）を有するリザーバを充填する好ましい方法である。例えば、注入を用いて異なるキャップ厚さを得るために、異なる量のキャップ材料が各個々のリザーバ中に注入されるか、または直接プリントされる。スピンコーティングは、浅い（10μmより浅い）リザーバ、基板を完全には貫通しないリザーバ、または小さな（100μmより小さい）開口を有するリザーバを充填する好ましい方法である。スピンコーティングによるキャップ厚さまたは材料の変化は、スピンコーティング、選択されたリザーバをマスクすること、およびエッチングの繰り返しの段階的なプロセスによって達成され得る。例えば、スピンコーティングでキャップの厚さを変化させるために、キャップ材料は、全基板にわたってスピンコーティングされる。必要ならば、材料がほぼプラナライズされるまで、スピンコーティングは繰り返される。フォトレジストのようなマスク材料が、１つを除くすべてのリザーバにおいてキャップ材料を覆うためにパターニングされる。プラズマ、イオンビーム、または化学的エッチング液は、所望の厚さに、露出されたリザーバにおいてキャップ材料をエッチングするために使用される。次いで、フォトレジストは、基板から取り除かれる。このプロセスは繰り返され、その間、フォトレジストの新たな層が、１つを除く全てのリザーバにおいてキャップ材料を覆うように堆積され、そしてパターニングされる（露出されたリザーバは、その所望の厚さにすでにエッチングされたリザーバと同じリザーバではない）。このリザーバにおける露出されたキャップ材料のエッチングは、所望のキャップ厚さが得られるまで続く。フォトレジストのようなマスク材料の堆積およびパタ

ーニング、

エッチング、およびマスク除去のこのプロセスは、各リザーバが、それ自体の固有のキャップ厚さを有するまで繰り返され得る。技術（UVフォトリソグラフィー、プラズマ、またはイオンビームエッチングなど）は、マイクロ製造の分野の当業者に周知である。

注入、インクジェットプリント、およびスピンコーティングは、キャップ製造の好ましい方法であるが、各リザーバは、毛管現象によって、真空または他の圧力勾配を用いて材料をリザーバ中に引くまたは押すことによって、材料をリザーバ中に融解することによって、遠心分離および関連するプロセスによって、固体をリザーバ中に手動でパックすることによって、またはこれらの技術かもしくは類似のリザーバ充填技術の任意の組合せによって、独立的にキャップされ得ることが理解される。

一旦キャップ製造方法が選択されると、リザーバからの分子の放出の時間を制御するためのさらなる方法が、利用され得る。２つの非限定的な例は、UV重合可能ポリマー、または放出システムおよびキャップ材料の層化のいずれかを含む。第１に、リザーバキャップが、注入されるか、インクジェットプリントされるか、またはスピンコーティングされるかのいずれかのUV重合可能ポリマーから作製される場合、各キャップは、異なる強度のUV光に露出され得、種々の程度の架橋、およびそれゆえ、分解性キャップについての異なる分解もしくは溶解の速度、または非分解性キャップについての分子に対する異なる透過性を与える。第２に、分解性および非分解性の両方のキャップ材料の層は、注入、インクジェットプリント、スピンコーティング、または選択的な架橋によって、送達されるべき分子を含む放出システムの層間で挿入され得る。これらの方法および他の類似の方法は、複雑な放出プロフィール（すなわち、不規則な時間間隔での脈動送達）が、単一のリザーバから達成されることを可能にする。

所望であれば、受動定時放出デバイスは、リザーバキャップなしで製造され得る。したがって、分子の放出の速度は、送達されるべき分子を含む放出システムの物理的および物質的性質によって単に制御される。

能動定時放出リザーバキャップの製造

好ましい実施態様では、フォトレジストが、絶縁性材料または誘電性材料の薄膜により被覆されたリザーバを有する基板の表面上で電極の形態でパターニングされる。フォトレジストは、リザーバの被覆された開口部の直上領域がフォトレジストによって被覆されていないままであり、そしてアノードの形状にあるように現像される。溶液中に溶解し得るか、または電位の印加の際に可溶性イオンまたは酸化化合物を形成し得る誘電性材料の薄いフィルムが、堆積技術（例えば、化学蒸着、電子ビームまたはイオンビームエバポレーション、スパッタリング、スピンコーティング、および当該分野で公知の他の技術）を用いて全表面の上に堆積される。例示の材料は、Kwonら（1991）およびBaeら（1994）により開示されるような、金属（例えば、銅、金、銀、および亜鉛）およびいくつかのポリマーを含む。フィルム堆積後、フォトレジストは、基板から剥がされる。これにより、フォトレジストにより被覆されていない領域を除いて、堆積されたフィルムが除かれる（リフトオフ技術）。これにより、電極３６０の形態で基板の表面上に誘電性材料が残される。代替的な方法は、デバイスの全表面上に誘電性材料を堆積させる工程、UVまたは赤外線（IR）フォトリソグラフィーを用いて誘電性フィルムの頂上部に、フォトレジストがアノードの形状でリザーバ上に位置するように、フォトレジストをパターニングする工程、およびプラズマ、イオンビーム、または化学エッチング技術を用いて、マスクされていない誘電性材料をエッチングする工程を包含する。次いで、フォトレジストを剥がし、リザーバを被覆する誘電性フィルムアノードを残す。誘電性材料の代表的なフィルム厚は、0.05～数ミクロンまでの範囲であり得る。アノードは、リザーバキャップとして働き、そしてデバイス上のカソードの配置は、デバイスの用途および電位制御の方法に依存する。

酸化シリコン（SiO_x）または窒化シリコン（SiN_x）のような絶縁性材料または誘電性材料は、化学蒸着（CVD）、電子ビームまたはイオンビームエバポレーション、スパッタリング、またはスピンコーティングのような方法によってデバイスの全表面上に堆積される。フォトレジストは、各リザーバ３８０の直上にある

カソードおよびアノードの一部を除いて、誘電体をエッチングから保護するために、その頂上にパターニングされる。誘電性材料は、プラズマ、イオンビーム、

または化学エッチング技術によりエッチングされ得る。このフィルムの目的は、電極フィルムが放出に必要でない全ての領域における腐食、分解、または溶解から電極を保護することである。

電極は、アノードとカソードとの間の電気が生じるとき、アノードリザーバキャップの非保護（誘電体によって被覆されていない）部分が酸化して、溶液中に溶解する可溶性化合物またはイオンを形成し、放出される分子を含む放出システムを周囲液に露出するように位置される。分子は、分解性の放出システムの分解または分離速度あるいは非分解性の放出システムからの分子の拡散の速度に依存する速度で、リザーバから放出される。

絶縁性膜（リザーバエッチストップ）の除去

リザーバ製造の間にマスクおよびエッチストップとして使用されるリザーバを被覆する絶縁性材料または誘電性材料の薄膜は、リザーバ４００の充填前に能動定時放出デバイスから、そして（リザーバが基板を完全に通している場合）リザーバ４４の充填後に受動定時放出デバイスから除去されなければならない。フィルムは２つの方法で除去され得る。第一には、フィルムは、イオンビームまたはリアクティブイオンプラズマによって除去され得る。好ましい実施態様では、絶縁性材料として用いられる窒化シリコンは、CHF_3またはCF_4のような酸素およびフッ素含有気体で構成されたリアクティブイオンプラズマによって除去され得る。第二には、フィルムは、化学エッチングにより除去され得る。例えば、緩衝化フッ化水素酸（BHFまたはBOE）が、シリコンジオキシドをエッチングするために用いられ得、そして熱リン酸が、窒化シリコンをエッチングするために用いられ得る。

リザーバ充填

送達用分子を含む放出システムは、注入、インクジェットプリント、またはスピンコーティングによって、リザーバの大きな開口部に挿入される（40a/40b/400）。各リザーバは、異なる分子および投与量を含み得る。同様に、各リザーバ

中の分子の放出速度論は、放出システムおよびキャップ材料の選択により変動さ

れ得る。さらに、各リザーバにおける放出システムおよびキャップ材料の混合または重層が、特定の適用の必要性に放出速度論を適合させるように用いられ得る。

送達される分子を含む放出システムが充填されたリザーバのマイクロチップの上の分布は、患者の医学的必要性またはシステムの他の要件に依存して変動し得る。薬物送達における適用のために、例えば、各列における薬物は、互いに異なり得る。１つの列はホルモンを含み得、そして別の列は代謝物を含み得る。また、放出システムは、各列内で、１つのリザーバからは高い速度でそして別のリザーバからは遅い速度で薬物を放出するように異なり得る。投与量はまた、各列内で変動し得る。深い（10μｍより大きい）リザーバまたは大きな（100μｍより大きい）開口部を有するリザーバを有するこれらのデバイスについて、リザーバローディングの差異は、各リザーバに直に異なる量の材料を注入またはインクジェットプリントすることにより達成され得る。リザーバ間の変動は、浅い（10μｍ未満）リザーバ、基板を完全に通過していないリザーバ、または小さい（100μｍ未満）の開口部を有するリザーバを有するデバイスにおいて、受動定時放出リザーバキャップのスピンコーティングによる製造について上述したように、選択されたリザーバのマスキング、スピンコーティング、およびエッチングの繰り返し段階状プロセスによって達成され得る。好ましくは、放出システムおよび送達される分子は、リザーバへの適用の前に送達および混合される。注入、インクジェットプリント、およびスピンコーティングがリザーバ充填の好ましい方法であるが、各リザーバは、キャピラリー作用、真空または他の圧力勾配を用いるリザーバへの材料の引き寄せまたは押し込み、リザーバへの材料の溶融、遠心分離および関連プロセス、リザーバへの固体の手動充填、またはこれらまたは同様のリザーバ充填技術の任意の組み合わせによって、個々に充填され得ることが理解される。

デバイスパッケージング、制御回路、および電源

受動リザーバおよび能動リザーバが充填されている開口部は、ウェハー結合ま

たは防水性エポキシまたは周囲液44/440に不透性の他の適切な材料によって密封されている。インビトロの適用については、全体のユニット、リザーバおよび電極を含むデバイスの正面を除いて、システムに適切な材料中に入れられる。インビボの適用については、ユニットは生体適合性材料（例えば、ポリ（エチレングリコール）またはポリテトラフルオロエチレン）中にカプセル化されている。

能動定時放出デバイスによる分子の放出についての機構は、撤回するかまたは取り除かなければならない互いに適合するかまたは接着した複数の部分に依存しない。各リザーバの放出時間の制御は、図３に示したように、予めプログラムしたマイクロプロセッサ、リモートコントロール、バイオセンサからの信号、またはこれらの方法の任意の組合せによって達成され得る。まず、マイクロプロセッサをメモリーのソース（例えば、プログラム可能な読み出し専用メモリ（PROM））、タイマー、デマルチプレクサ、および電源（例えば、マイクロ電池）と共に使用される。これは、例えば、Jonesら（1995）およびBatesら（1992）によって記載される。放出パターンは、使用者によりPROMに直接書き込まれる。PROMは、これらの指示をマイクロプロセッサにを送る。放出の時間がタイマーによって指示される時間に達した場合、マイクロプロセッサは、デマルチプレクサへの特定のリザーバのアドレス（場所）に対応する信号を送る。デマルチプレクサは、インプット（例えば、電位）をマイクロプロセッサによってアドレスづけられたリザーバに送る。マイクロ電池は、PROM、タイマー、およびマイクロプロセッサを操作するための電源を提供し、そしてデマルチプレクサにより特定のリザーバに指向される電位インプットを提供する。これらの構成要素の各々の製造、大きさ、および場所は、特定の適用の要件に依存する。好ましい実施態様において、メモリ、タイマー、マイクロプロセッサ、およびデマルチプレクサ回路は、チップの表面上に直接組み込まれる。マイクロ電池は、チップの反対面に接着しており、そしてデバイス回路にバイアまたは薄いワイヤにより連結されている。しかし、いくつかの場合、メモリー、タイミング、プロセシング、およびデマルチプレキシングについて、別々の、予め作製したコンポーネントチップを使用することも可能である。これらは、電池が付いたミニチュア化送達デバイスの背面に接着

している。使用される予め作製したチップの大きさおよび型は送達デバイスの全体の寸法およびリザーバの数に依存する。第二に、特定のリザーバの電位の適用による活性化は、リモートコントロールにより外的に制御される。リモートコントロールに使用される回路の多くは、予めプログラムされた方法に使用されるものと同一である。主要な差違は、PROMが信号レシーバによって置換されていることである。ラジオ波、低出力レーザ、または超音波のような信号は、外部ソースによりレシーバ（例えば、コンピュータ、または超音波生成器）に送られる。信号はマイクロプロセッサに送られ、ここでこれはリザーバアドレスに翻訳される。次いで、電力はデマルチプレクサを通って適切なアドレスを有するリザーバへと指向される。第三に、バイオセンサをマイクロチップに組み込み、周囲液中の分子を検出する。分子の濃度が特定のレベルに達する場合、センサはマイクロプロセッサに信号を送り、１つ以上のリザーバを活性化する。マイクロプロセッサは、特定の電力をデマルチプレクサを通してリザーバ（単数または複数）へと指向させる。

電位制御法

活性型デバイスリザーバキャップはアノードであり、これは電位がアノードとカソードとの間に適用される場合、酸化して可溶性化合物およびイオンを形成する。所定の電極材料および電解質について、これらの酸化反応が熱力学的および動力学的に好ましい電位の範囲が存在する。デバイスのリザーバキャップを再現性よく酸化し、そして開けるために、アノード電位は、この電位の範囲に維持されなければならない。

２つの特定の電位範囲の電極を維持する２つの主要な制御方法が存在する。第一の方法は、定電位制御と呼ばれる。名称が示すように、電位は、リザーバ活性化の間、一定に保たれる。電位の制御は、代表的に参照電極と呼ばれる既知の一定電位を有する第三の電極を系へ組み込むことにより達成される。参照電極は、外部プローブの形態を取り得、その先端がアノード表面から１～３mm以内に配置される。アノードの電位は、飽和カロメル電極（SCE）のような参照電極の既知の電位を参照して測定され制御される。定電位制御の好ましい実施態様において

、薄層フィルム参照電極および電位フィードバック制御回路がマイクロチップの表面に直接構成され得る。例えば、マイクロチップデバイスとともに組み込まれた微小構成されたAg/AgCl参照電極は、酸化レジーム内でリザーバが完全に開くま

でデバイスが活性化リザーバのアノード電位を維持することを可能にする。第二の方法は定電流制御と呼ばれる。名称が示すように、電流がリザーバ活性化の間一定に保たれる。この制御の方法の１つの欠陥は、所定の電流密度に対して１つを超える安定電位が存在することである。しかし、電流密度対電位の挙動が特定の電解質系におけるマイクロチップデバイスについて十分に特徴づけられる場合、酸化レジームにおけるアノードを維持する電流密度は、明らかになる。この場合、電位制御の定電流法は、定電位制御よりも好ましい。なぜなら、定電流制御は参照電極を必要としないからである。

マイクロチップ適用

受動および能動のマイクロチップデバイスは、多数のインビトロおよびインビボの適用を有する。マイクロチップは、正確に制御された時間および速度で溶液または反応混合物へインビトロで小さな制御された量の化学試薬または他の分子を送達するために使用され得る。分析化学およっび医学的診断は、マイクロチップ送達デバイスが使用され得る分野の例である。マイクロチップは、インビボで薬物送達デバイスとして使用され得る。マイクロチップは、外科技術または注射のいずれかにより患者に移植され得るか、あるいは嚥下され得る。マイクロチップは、医薬品を飲むことを覚えられないかまたは十分に移動し得ない動物またはヒトへの薬物の送達を提供する。マイクロチップは、異なる送達速度および異なる回数での多くの異なる薬物の送達をさらに提供する。

本発明は、以下の非限定的な実施例を参照することによってさらに理解される。

実施例１：受動定時薬物放出を伴うマイクロチップ

受動定時放出デバイス、マイクロチップ10を図４に示す。マイクロチップ10は、基板14から形成される。リザーバ16は、基板14にエッチングされている。リザ

ーバ16に配置されているのは送達のための分子18を含有する放出システムである。リザーバはリザーバキャップ12で蓋がされている。放出システムおよび送達のための分子18は、列20a、20b,,20cの間、および各々の列のリザーバ内で変化し得る。

マイクロチップ10は、インビトロ適用のための溶液に挿入され得るか、または身体の選択された部分に移植され得るか、またはインビボ適用のために嚥下され得、そしてさらなる監視を必要とすることなく放置して作動させられ得る。周囲液に曝される場合、リザーバキャップ12は分解し、溶解し、または送達のための分子18を含有する放出システムにたいして透過性になる。

図7a～iは、受動送達デバイスのためのいくつかのさらなる潜在的な構成を示す。

実施例２：能動制御時間放出を伴うマイクロチップ

能動定時放出を提供する薬物送達デバイスを図５のマイクロチップ100に示す。マイクロチップ100は、マイクロチップ100は、能動定時放出を提供する電極を含むことを除いて、マイクロチップ10に類似する。マイクロチップ100は、基板160、送達のための分子180を含有する放出システム、アノードリザーバキャップ120、およびカソード140から形成される。好ましくは、マイクロチップ100は、インプット源、マイクロプロセッサ、タイマー、デマルチプレクサ、および電源（示していない）をさらに含む。電源は、反応を選択したアノードとカソードとの間の反応を駆動するためのエネルギーを提供する。アノードとカソードとの間小さな電位の適用の際に、電子はアノードからカソードへ外部回路を通って通過して、アノード材料を酸化し、そして可溶性の化合物またはイオンを形成し、周囲液に溶解し、送達のための分子180を含有する放出システムを周囲液へ露出する。マイクロプロセッサはPROM、リモートコントロール、またはバイオセンサによって指示されるようにデマルチプレクサを通って特定の電極対へと電力を指向させる。

図６は、アノードとカソードとの間の電位の適用の際にデバイスから能動的に薬物280を放出する、基板260由来のマイクロチップ200の第二の実施態様の模式

図である。これは、図５のデバイスとは異なり、絶縁体オーバーレイヤを含む。

図８ａ～ｃは、能動送達デバイスについての３つのさらなる潜在的な構成を示す。

【図１】

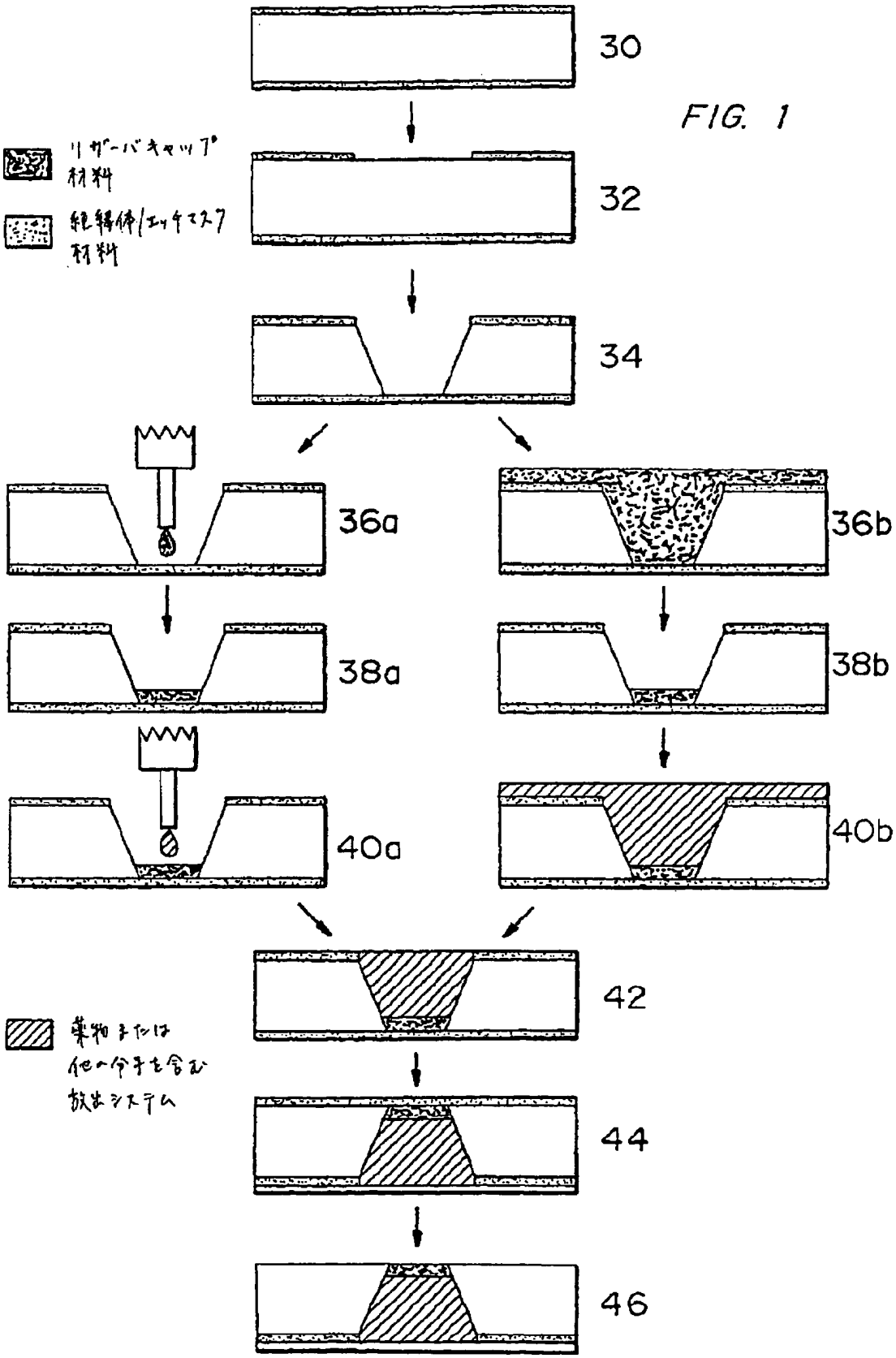

30
32
34
36a
36b
38a
38b
40a
40b
42
44
46
リガーバキャップ材料
絶縁体/エッチマスク材料
薬物または他の分子を含む放出システム

FIG. 1

【図２】

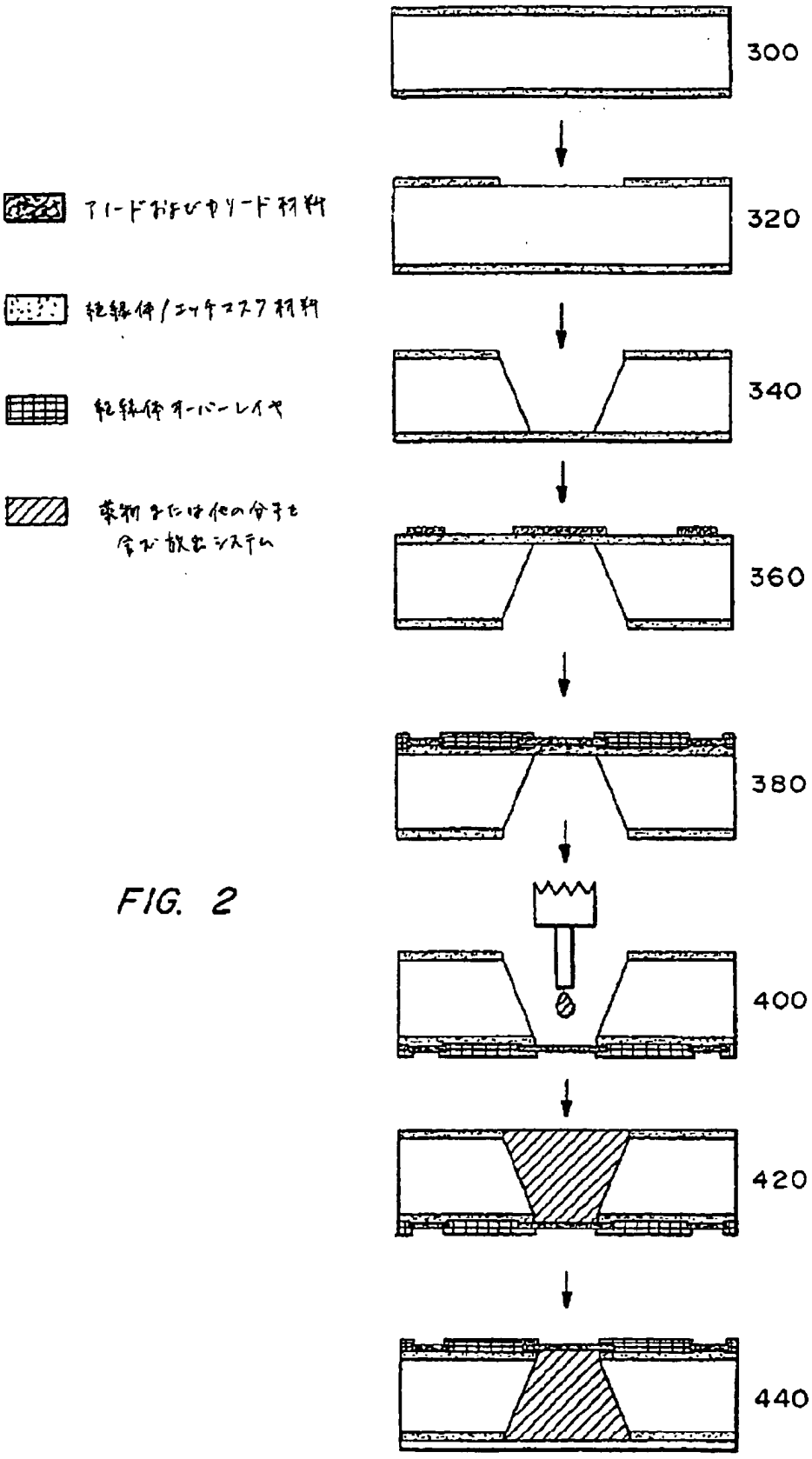

アノードおよびカソード材料
絶縁体/エッチマスク材料
絶縁体オーバーレイヤ
薬物または他の分子を含む放出システム
300
320
340
360
380
400
420
440

FIG. 2

【図３】

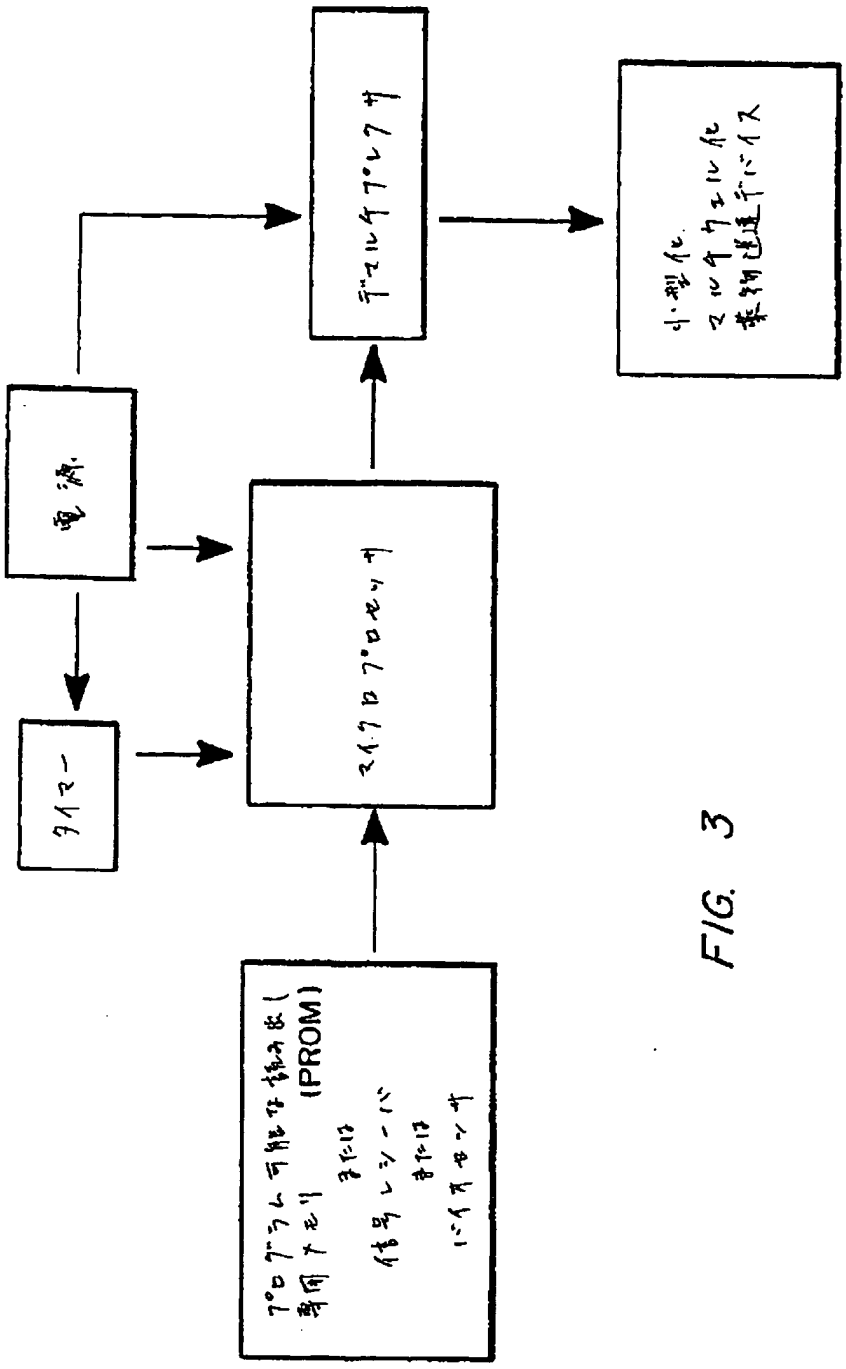

電源
タイマー
プログラム可能な読出し専用メモリ (PROM)
データ
信号レシーバ
データ
インタセンサ
デバイスアクチュエータ
小型化マイクロフェルデバイス

FIG. 3

【図４】

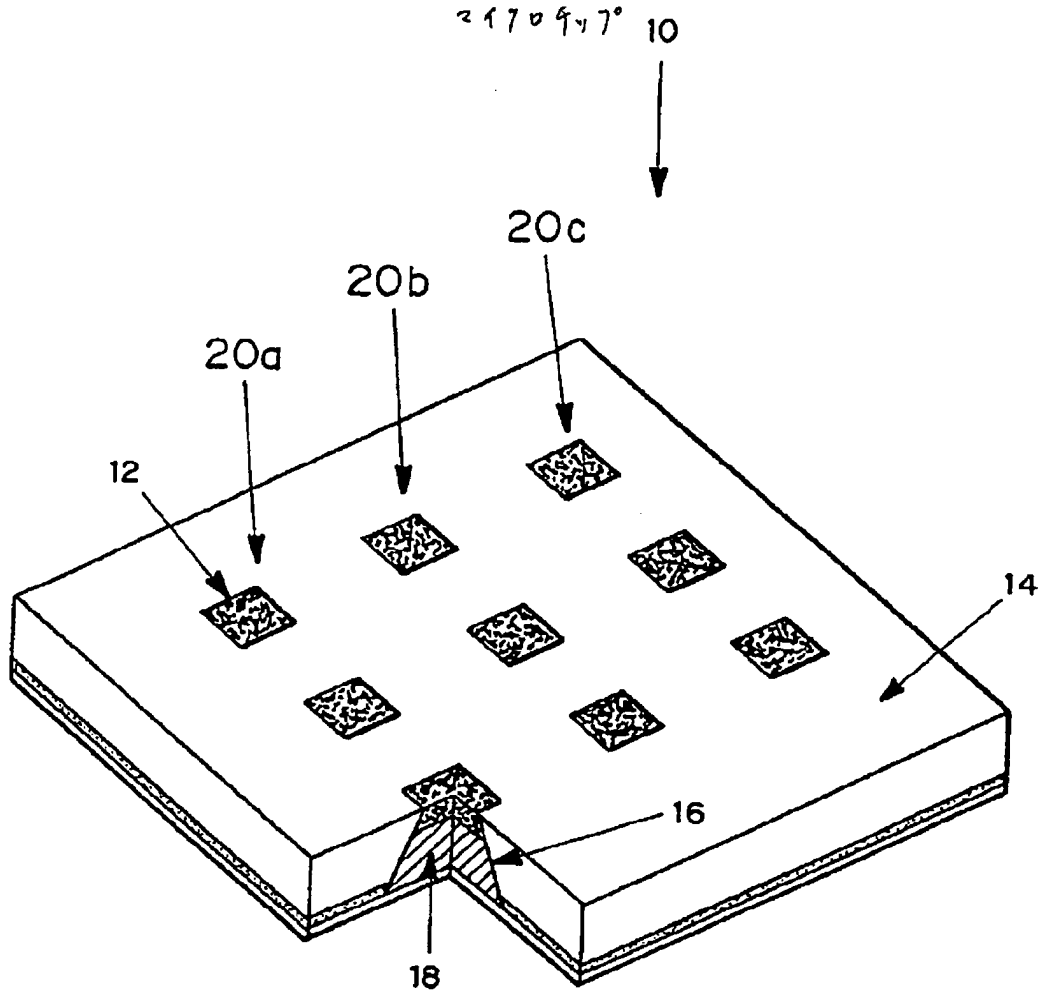

マイクロチップ 10
20c
20b
20a
12
14
16
18
薬物または他の分子を含む放出システム
リザーバキャップ材料
絶縁体/エッチマスク材料

FIG. 4

【図５】

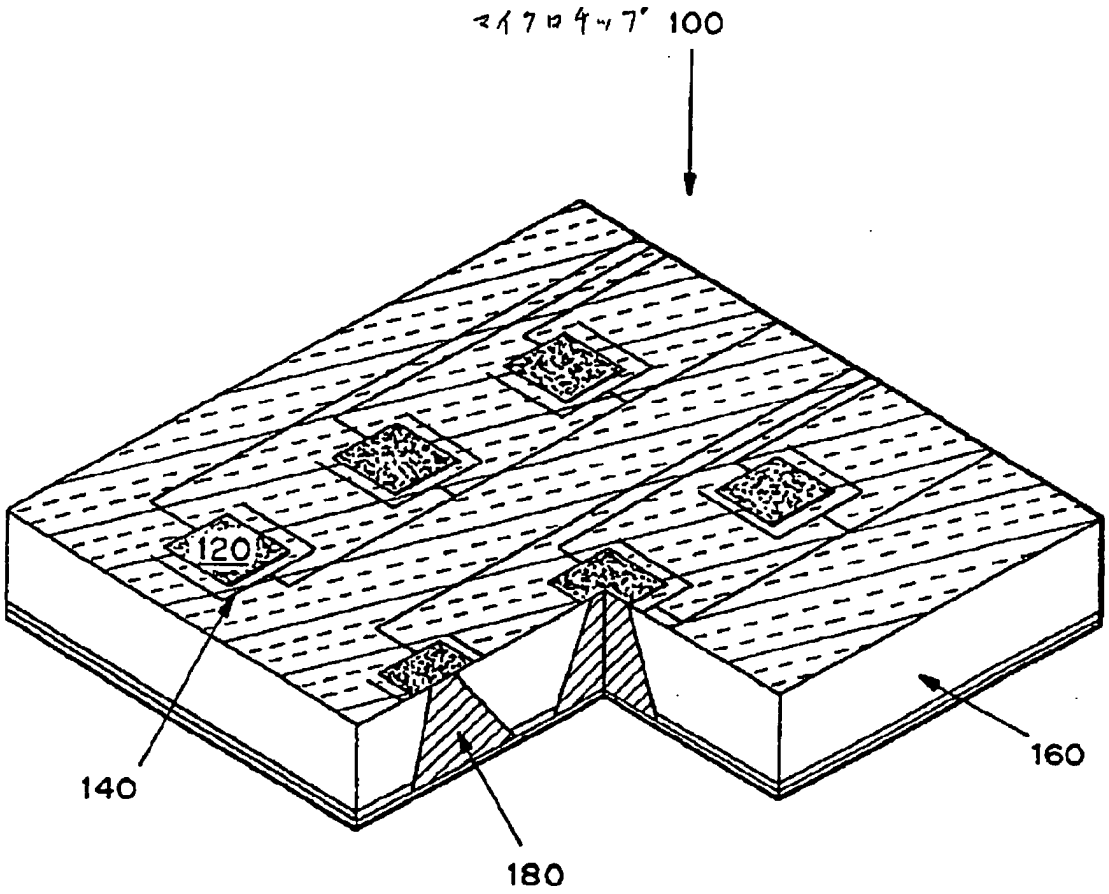

マイクロチップ 100
120
140
160
180
薬物または他の分子を含む放出システム
アノードおよびカソード材料
絶縁体/エッチマスク材料

FIG. 5

【図６】

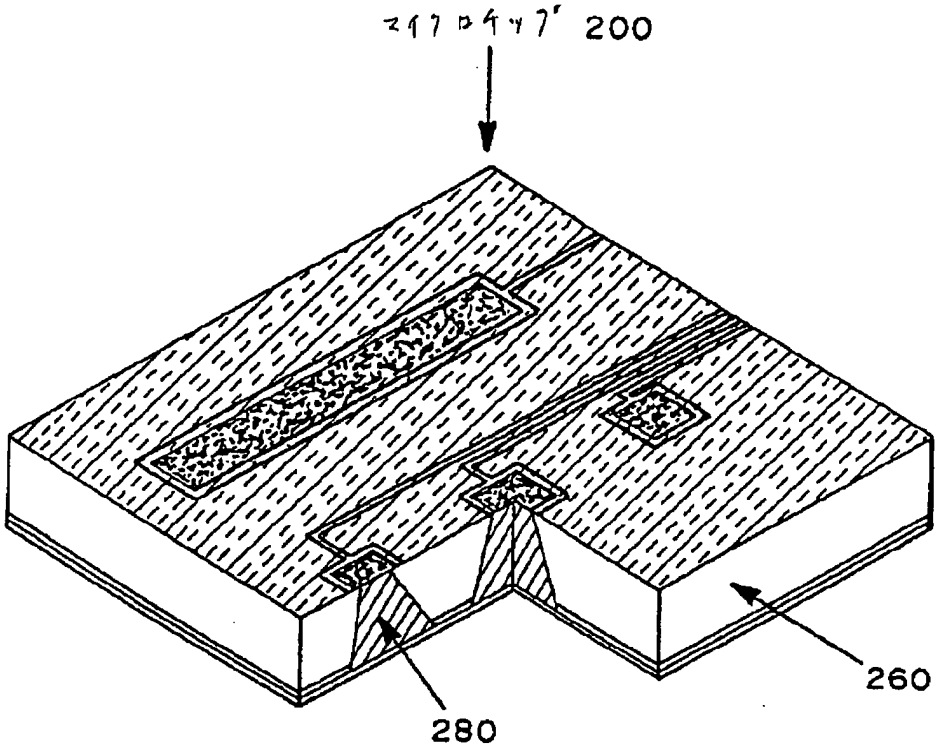

マイクロチップ 200
260
280
薬物または他の分子を含む放出システム
アノードおよびカソード材料
絶縁体オーバーレイヤおよびエッチマスク材料

FIG. 6

【図７】

FIG. 7a

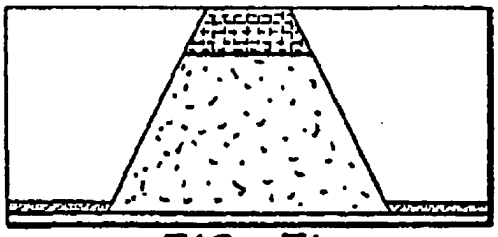


FIG. 7e

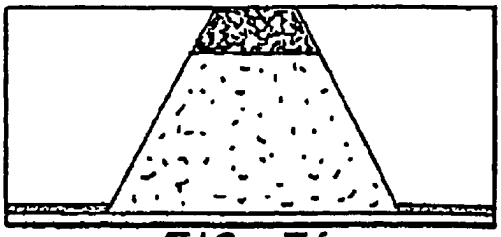


FIG. 7b

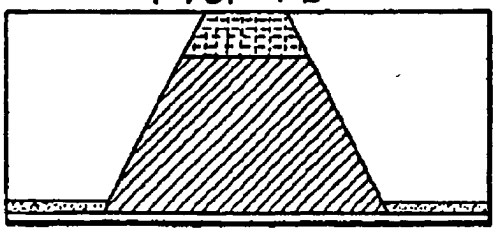


FIG. 7f

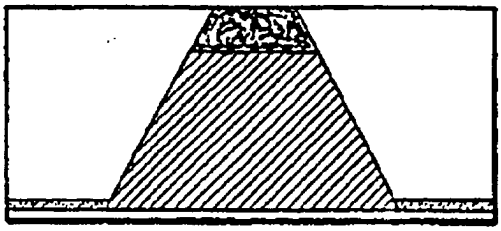


FIG. 7c

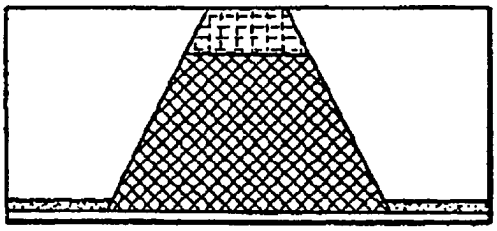


FIG. 7g

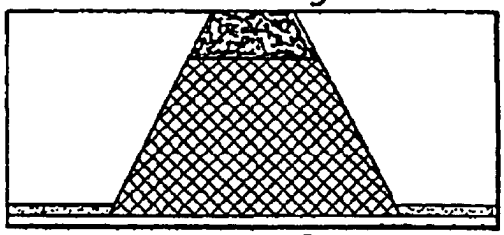


FIG. 7d

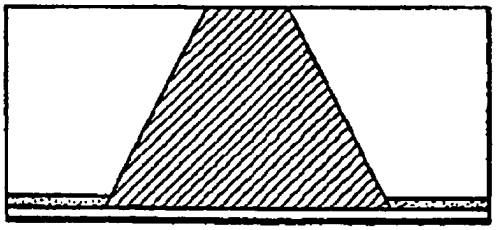


FIG. 7h

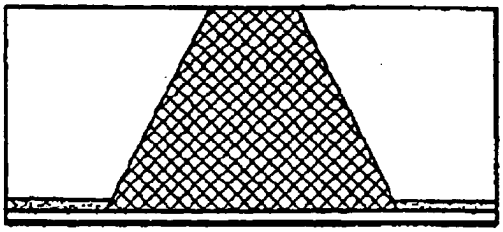
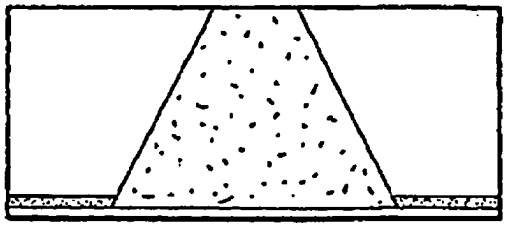
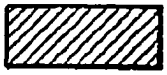


FIG. 7i



分解性リザーバキャップ材料

非分解性リザーバキャップ材料



分解性放出システム

非分解性放出システム

純粋物または他の分子（固体、液体、またはゲル形態）

絶縁体／エッチマスク材料

【図８】

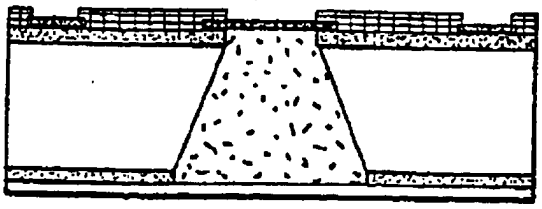


FIG. 8a

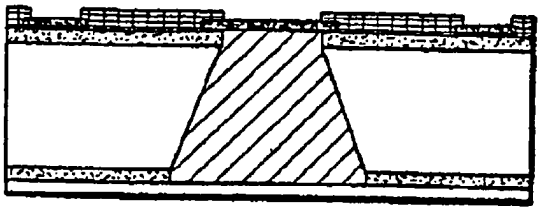


FIG. 8b

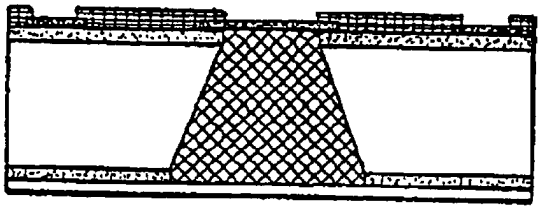
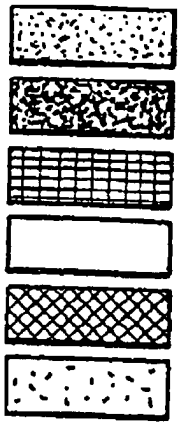


FIG. 8c



【国際調査報告】

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 97/11589

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 03790 A (RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY) 4 March 1993 see the whole document	1-35
A	US 5 042 975 A (YIE, W. CHIEN, ET AL.) 27 August 1991 see the whole document	1-35
A	US 4 731 049 A (EDGARDO J. PARSI) 15 March 1988 see the whole document	1-35

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 April 1998	21/04/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ...nal Application No
PCT/US 97/11589

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9303790 A	04-03-93	AU 2563292 A	16-03-93
		CA 2122150 A	04-03-93
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		JP 7501238 T	09-02-95
US 5042975 A	27-08-91	AT 143278 T	15-10-96
		AU 7751387 A	24-02-88
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		DE 3751917 T	20-03-97
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		EP 0316342 A	24-05-89
		JP 2500487 T	22-02-90
		KR 9508027 B	24-07-95
		WO 8800846 A	11-02-88
US 4731049 A	15-03-88	NONE	

フロントページの続き

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ドイツ国 デー―91052 アーランゲン，クリスチャン―アーンスト―ストラーセ 30

【公報種別】特許法第１７条第１項及び特許法第１７条の２の規定による補正の掲載
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【発行日】平成１３年４月１７日（２００１．４．１７）

【公表番号】特表２０００－５１３７２５（Ｐ２０００－５１３７２５Ａ）
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【国際特許分類第７版】
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9/52
【ＦＩ】
A61K 9/00
9/52

手続補正書

平成１２年１０月３１日

特許庁長官 殿

１．事件の表示
平成１０年特許願第５０４４６０号

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電話（大阪）０６－６９４９－３９１０

４．補正対象書類名
請求の範囲

５．補正対象項目名
請求の範囲

６．補正の内容
請求の範囲を別紙のとおり補正します。

請求の範囲

１．分子の放出のためのマイクロチップデバイスであって，
基板および
該基板上の複数のリザーバを備え，ここで該リザーバがその中に組み込まれている分子を制御可能に放出する，マイクロチップデバイス。

２．前記リザーバが，異なるタイプの分子，異なる量の分子，またはそれらの組合せを含む，請求項１に記載のデバイス。

３．前記分子の放出が，前記リザーバ中に分子を組み込む放出システムにより制御される，請求項１に記載のデバイス。

４．前記放出システムの上の前記リザーバに位置した分解性リザーバキャップをさらに備え，ここで前記キャップの分解または溶解速度が，分子が該リザーバから放出される時間を決定する，請求項３に記載のデバイス。

５．前記リザーバキャップが異なる厚さを有する，請求項４に記載のデバイス。

６．前記リザーバキャップが分解または溶解された後，リザーバ中の前記放出システムが分解または溶解し，前記分子を放出する，請求項４に記載のデバイス。

７．前記分子が，拡散様式または特殊様式で放出される，請求項１に記載のデバイス。

８．前記放出が，１つのリザーバ中に異なる放出システムおよびリザーバキャップ材料を組合せることにより，該リザーバから得られる，請求項４に記載のデバイス。

９．前記放出システムが非分解性であり、そして前記分子の該放出システムからの拡散が、前記リザーバキャップの分解後に該分子の原動放出を提供する、請求項４に記載のデバイス。

１０．放出システムの上のリザーバ上に位置した非分解性リザーバキャップを備え、前記分子のキャップを通じる拡散速度が、該分子がリザーバから放出される速度を決定する、請求項３に記載のデバイス。

１１．カソード、マイクロプロセッサ、タイマー、デマルチプレクサ、および電源をさらに備え、ここで該リザーバキャップがアノードであり、そしてそれぞれ該カソードの１つによって囲まれ、ここで各カソードとアノードとの間の電位の印加の際に、該リザーバキャップが酸化し、該放出中に溶解し、そして下にある放出システムを周囲液に露出する、請求項４に記載のデバイス。

１２．前記マイクロプロセッサ機能が、特定の時間で個々のリザーバの電極を活性化させるように予めプログラムされたメモリソースにより指示される、請求項１１に記載のデバイス。

１３．前記マイクロプロセッサ機能が、各リザーバの電極を活性化させるようにリモートコントロールにより指示される、請求項１１に記載のデバイス。

１４．バイオセンサをさらに備え、ここで前記マイクロプロセッサ機能が、各リザーバの電極を活性化するように該バイオセンサにより指示される、請求項１１に記載のデバイス。

１５．前記放出システムが医薬剤または診断剤中に薬物分子を含む、請求項２に記載のデバイス。

１６．前記分子が薬物であり、前記マイクロチップが患者に投与されるか、移植されるか、または注入される、請求項１に記載のデバイス。

１７．前記分子が、抗原、タンパク質、アミノ酸、多糖、および有機分子または合成分子からなる群から選択される薬物である、請求項１６に記載のデバイス。

１８．前記薬物が、薬学的に受容可能なキャリアと混ぜ合わされている、請求項１７に記載のデバイス。

１９．前記分子が診断試薬または化学試薬である、請求項１に記載のデバイス。

２０．各リザーバ中の前記放出システムが、放出される分子で形成され、ここで該分子の溶解速度が該分子の放出速度を決定する、請求項１５に記載のデバイス。

２１．分子の放出のためのデバイスを製造する方法であって、
基板を提供する工程；
エッチマスクとして使用するために、該基板上に絶縁性材料を堆積させ、そしてパターニングする工程；
該基板中に複数のリザーバをエッチングする工程；
該リザーバに放出システムおよびキャップ材料を充填する工程；および
該放出システムおよびキャップ材料をエッチングする工程
を包含する、方法。

２２．前記リザーバの上の絶縁性材料の薄いフィルムを取り除く工程をさらに包含する、請求項２１に記載の方法。

２３．各リザーバを、異なるタイプおよび量のキャップ材料および、送達される分子を含む放出システムで充填する工程をさらに包含する、請求項２１に記載の方法。

２４．前記リザーバが、注入、インクジェットプリント、またはスピンコーティングによって充填される、請求項２１に記載の方法。

２５．前記リザーバが、インクジェットプリントによって充填される、請求項２４に記載の方法。

２６．各リザーバの上の絶縁性材料の薄いフィルムの上に導電性材料の薄いフィルムを堆積させる工程をさらに包含する、請求項２２に記載の方法。

２７．アノードが各リザーバーの開口部を被覆し、そしてカソードが各アノードの周辺にあるように、該導電性フィルムを電極にパターニングする工程をさらに包含する、請求項２６に記載の方法。

２８．前記アノードが前記リザーバの上にあり、そして前記カソードが該アノードの露出された部分の周囲にあることを除いて、各電極の上に材料を堆積させる工程をさらに包含する、請求項２７に記載の方法。